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- (71) Applicant (for all designated States except US): **GENENTECH, INC.** [US/US]; 1 DNA Way, South San Francisco, CA 94080-4990 (US).
- (71) Applicants and
- (72) Inventors: **BAKER, Kevin, P.** [GB/US]; 14006 Indian Run Drive, Darnestown, MD 20878 (US). **FERRARA, Napoleone** [US/US]; #704, 2090 Pacific Avenue, San Francisco, CA 94109 (US). **GERBER, Hanspeter** [CH/US]; #5, 1121 Tennessee Street, San Francisco, CA 94107 (US). **GERRITSEN, Mary, E.** [CA/US]; 541 Parrott Drive, San Mateo, CA 94402 (US). **GODDARD, Audrey** [CA/US]; 110 Congo Street, San Francisco, CA 94131 (US). **GODOWSKI, Paul, J.** [US/US]; 2627 Easton Drive, Burlingame, CA 94010 (US). **GURNEY, Austin, L.** [US/US]; 1 Debbie Lane, Belmont, CA 94002 (US). **HILLAN, Kenneth, J.** [GB/US]; 64 Seward Street, San Francisco, CA 94114 (US). **MARSTERS, Scot, A.** [US/US]; 990 Cherry Street, San Carlos, CA 94070 (US). **PAN, James** [CA/US]; 2705 Coronet Boulevard, Belmont, CA 94002 (US). **PAONI, Nicholas, F.** [US/US]; 1756 Terrace Drive, Belmont, CA 94002 (US). **STEPHAN, Jean-Philippe, F.** [FR/US]; 320 C Lansdale Avenue, Millbrae, CA 94030 (US). **WATANABE, Colin, K.** [US/US]; 128 Corliss Drive, Moraga, CA 94556 (US). **WILLIAMS, P., Mickey** [US/US]; 509 Alto Avenue, Half Moon Bay, CA 94019 (US). **WOOD, William, L.** [US/US]; 35 Southdown Court, Hillsborough, CA 94010 (US).
- (72) Inventor; and
- (75) Inventor/Applicant (for US only): **YE, Weilan** [CN/US]; 119 Barkentine Street, Foster City, CA 94404 (US).

[Continued on next page]

(54) Title: **COMPOSITIONS AND METHODS FOR THE DIAGNOSIS AND TREATMENT OF DISORDERS INVOLVING ANGIOGENESIS**

(57) Abstract: Compositions and methods are disclosed for stimulating or inhibiting angiogenesis and/or cardiovascularization in mammals, including humans. Pharmaceutical compositions are based on polypeptides or antagonists thereto that have been identified for one or more of these uses. Disorders that can be diagnosed, prevented, or treated by the compositions herein include trauma such as wounds, various cancers, and disorders of the vessels including atherosclerosis and cardiac hypertrophy. In addition, the present invention is directed to novel polypeptides and to nucleic acid molecules encoding those polypeptides. Also provided herein are vectors and host cells comprising those nucleic acid sequences, chimeric polypeptide molecules comprising the polypeptides of the present invention fused to heterologous polypeptide sequences, antibodies which bind to the polypeptides of the present invention and to methods for producing the polypeptides of the present invention.

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(74) Agents: AGARWAL, Atulya, R. et al.; c/o Genentech, Inc., MS49, 1 DNA Way, South San Francisco, CA 94080-4990 (US).

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## COMPOSITIONS AND METHODS FOR THE DIAGNOSIS AND TREATMENT OF DISORDERS INVOLVING ANGIOGENESIS

### 1. Field of the Invention

The present invention relates to compositions and methods useful for the modulation (e.g., promotion or inhibition) of angiogenesis and/or cardiovascularization in mammals in need of such biological effect. The present invention further relates to the diagnosis and treatment of disorders involving angiogenesis (e.g., cardiovascular as well as oncological disorders).

### 2. Background of the Invention

#### 2.1. Angiogenesis

Angiogenesis, defined as the growth or sprouting of new blood vessels from existing vessels, is a complex process that primarily occurs during embryonic development. Under normal physiological conditions in adults, angiogenesis takes place only in very restricted situations such as hair growth and wounding healing (Auerbach, W. and Auerbach, R., 1994, *Pharmacol Ther* 63(3):265-311; Ribatti et al., 1991, *Haematologica* 76(4):311-20; Risau, 1997, *Nature* 386(6626):671-4). Unregulated angiogenesis has gradually been recognized to be responsible for a wide range of disorders, including, but not limited to cardiovascular disease, cancer, rheumatoid arthritis, psoriasis and diabetic retinopathy (Folkman, 1995, *Nat Med* 1(1):27-31; Isner, 1999, *Circulation* 99(13):1653-5; Koch, 1998, *Arthritis Rheum* 41(6):951-62; Walsh, 1999, *Rheumatology (Oxford)* 38(2):103-12; Ware and Simons, 1997, *Nat Med* 3(2):158-64).

#### 2.2. Cardiac Disorders and Factors

Heart failure affects approximately five million Americans, and new cases of heart failure number about 400,000 each year. It is the single most frequent cause of hospitalization for people age 65 and older in the United States. Recent advances in the management of acute cardiac diseases, including acute myocardial infarction, are resulting in an expanding patient population that will eventually develop chronic heart failure. From 1979 to 1995, hospitalizations for congestive heart failure (CHF) rose from 377,000 to 872,000 (a 130 percent increase) and CHF deaths increased 116 percent.

CHF is a syndrome characterized by left ventricular dysfunction, reduced exercise tolerance, impaired quality of life, and markedly shortened life expectancy. The sine qua non of heart failure is an inability of the heart to pump blood at a rate sufficient to meet the metabolic needs of the body's tissues (in other words, there is insufficient cardiac output).

At least four major compensatory mechanisms are activated in the setting of heart failure to boost cardiac output, including peripheral vasoconstriction, increased heart rate, increased cardiac contractility, and increased plasma volume. These effects are mediated primarily by the sympathetic nervous system and the renin-angiotensin system. See, Eichhorn, American Journal of Medicine, 104: 163-169 (1998). Increased output from the

sympathetic nervous system increases vascular tone, heart rate, and contractility. Angiotensin II elevates blood pressure by 1) directly stimulating vascular smooth muscle contraction, 2) promoting plasma volume expansion by stimulating aldosterone and antidiuretic hormone secretion, 3) stimulating sympathetic-mediated vascular tone, and 4) catalyzing the degradation of bradykinin, which has vasodilatory and natriuretic activity. *See*, review by Brown and Vaughan, Circulation, **97**: 1411-1420 (1998). As noted below, angiotensin II may also have directly deleterious effects on the heart by promoting myocyte necrosis (impairing systolic function) and intracardiac fibrosis (impairing diastolic and in some cases systolic function). *See*, Weber, Circulation, **96**: 4065-4082 (1998).

A consistent feature of congestive heart failure (CHF) is cardiac hypertrophy, an enlargement of the heart that is activated by both mechanical and hormonal stimuli and enables the heart to adapt to demands for increased cardiac output. Morgan and Baker, Circulation, **83**: 13-25 (1991). This hypertrophic response is frequently associated with a variety of distinct pathological conditions such as hypertension, aortic stenosis, myocardial infarction, cardiomyopathy, valvular regurgitation, and intracardiac shunt, all of which result in chronic hemodynamic overload.

Hypertrophy is generally defined as an increase in size of an organ or structure independent of natural growth that does not involve tumor formation. Hypertrophy of the heart is due either to an increase in the mass of the individual cells (myocytes), or to an increase in the number of cells making up the tissue (hyperplasia), or both. While the enlargement of an embryonic heart is largely dependent on an increase in myocyte number (which continues until shortly after birth), post-natal cardiac myocytes lose their proliferative capacity. Further growth occurs through hypertrophy of the individual cells.

Adult myocyte hypertrophy is initially beneficial as a short term response to impaired cardiac function by permitting a decrease in the load on individual muscle fibers. With severe, long-standing overload, however, the hypertrophied cells begin to deteriorate and die. Katz, "Heart Failure", in: Katz A.M. ed., Physiology of the Heart (New York: Raven Press, 1992) pp. 638-668. Cardiac hypertrophy is a significant risk factor for both mortality and morbidity in the clinical course of heart failure. Katz, Trends Cardiovasc. Med., **5**: 37-44 (1995). For further details of the causes and pathology of cardiac hypertrophy *see, e.g.*, Heart Disease. A Textbook of Cardiovascular Medicine, Braunwald, E. ed. (W.B. Saunders Co., 1988), Chapter 14, "Pathophysiology of Heart Failure."

On a cellular level, the heart is composed of myocytes and surrounding support cells, generically called non-myocytes. While non-myocytes are primarily fibroblast/mesenchymal cells, they also include endothelial and smooth muscle cells. Indeed, although myocytes make up most of the adult myocardial mass, they represent only about 30% of the total cell numbers present in heart. In response to hormonal, physiological, hemodynamic, and pathological stimuli, adult ventricular muscle cells can adapt to increased workloads through the activation of a hypertrophic process. This response is characterized by an increase in myocyte cell size and contractile protein content of individual cardiac muscle cells, without concomitant cell division and activation of embryonic genes, including the gene for atrial natriuretic peptide (ANP). Chien *et al.*, FASEB J., **5**: 3037-3046 (1991); Chien *et al.*, Annu. Rev. Physiol., **55**: 77-95 (1993). An increment in myocardial mass as a result of an increase in myocyte size that is associated with an accumulation of interstitial collagen within the extracellular matrix and around intramyocardial coronary arteries has been described in left ventricular hypertrophy secondary to pressure overload



in humans. Caspari *et al.*, Cardiovasc. Res., **11**: 554-558 (1977); Schwarz *et al.*, Am. J. Cardiol., **42**: 895-903 (1978); Hess *et al.*, Circulation, **63**: 360-371 (1981); Pearlman *et al.*, Lab. Invest., **46**: 158-164 (1982).

It has also been suggested that paracrine factors produced by non-myocyte supporting cells may additionally be involved in the development of cardiac hypertrophy, and various non-myocyte derived hypertrophic factors, such as, leukocyte inhibitory factor (LIF) and endothelin, have been identified. Metcalf, Growth Factors, **7**: 169-173 (1992); Kurzrock *et al.*, Endocrine Reviews, **12**: 208-217 (1991); Inoue *et al.*, Proc. Natl. Acad. Sci. USA, **86**: 2863-2867 (1989); Yanagisawa and Masaki, Trends Pharm. Sci., **10**: 374-378 (1989); U.S. Patent No. 5,573,762 (issued November 12, 1996). Further exemplary factors that have been identified as potential mediators of cardiac hypertrophy include cardiotrophin-1 (CT-1) (Pennica *et al.*, Proc. Nat. Acad. Sci. USA, **92**: 1142-1146 (1995)), catecholamines, adrenocorticosteroids, angiotensin, and prostaglandins.

At present, the treatment of cardiac hypertrophy varies depending on the underlying cardiac disease. Catecholamines, adrenocorticosteroids, angiotensin, prostaglandins, LIF, endothelin (including endothelin-1, -2, and -3 and big endothelin), and CT-1 are among the factors identified as potential mediators of hypertrophy. For example, beta-adrenergic receptor blocking drugs (beta-blockers, *e.g.*, propranolol, timolol, tertalolol, carteolol, nadolol, betaxolol, penbutolol, acetobutolol, atenolol, metoprolol, carvedilol, etc.) and verapamil have been used extensively in the treatment of hypertrophic cardiomyopathy. The beneficial effects of beta-blockers on symptoms (*e.g.*, chest pain) and exercise tolerance are largely due to a decrease in the heart rate with a consequent prolongation of diastole and increased passive ventricular filling. Thompson *et al.*, Br. Heart J., **44**: 488-98 (1980); Harrison *et al.*, Circulation, **29**: 84-98 (1964). Verapamil has been described to improve ventricular filling and probably reducing myocardial ischemia. Bonow *et al.*, Circulation, **72**: 853-64 (1985).

Nifedipine and diltiazem have also been used occasionally in the treatment of hypertrophic cardiomyopathy. Lorell *et al.*, Circulation, **65**: 499-507 (1982); Betocchi *et al.*, Am. J. Cardiol., **78**: 451-457 (1996). However, because of its potent vasodilating properties, nifedipine may be harmful, especially in patients with outflow obstruction. Disopyramide has been used to relieve symptoms by virtue of its negative inotropic properties. Pollick, N. Engl. J. Med., **307**: 997-999 (1982). In many patients, however, the initial benefits decrease with time. Wigle *et al.*, Circulation, **92**: 1680-1692 (1995). Antihypertensive drug therapy has been reported to have beneficial effects on cardiac hypertrophy associated with elevated blood pressure. Examples of drugs used in antihypertensive therapy, alone or in combination, are calcium antagonists, *e.g.*, nitrendipine; adrenergic receptor blocking agents, *e.g.*, those listed above; angiotensin converting enzyme (ACE) inhibitors such as quinapril, captopril, enalapril, ramipril, benazepril, fosinopril, and lisinopril; diuretics, *e.g.*, chlorothiazide, hydrochlorothiazide, hydroflumethazide, methylchlorothiazide, benzthiazide, dichlorphenamide, acetazolamide, and indapamide; and calcium channel blockers, *e.g.*, diltiazem, nifedipine, verapamil, and nicardipine.

For example, treatment of hypertension with diltiazem and captopril showed a decrease in left ventricular muscle mass, but the Doppler indices of diastolic function did not normalize. Szlachcic *et al.*, Am. J. Cardiol., **63**: 198-201 (1989); Shahi *et al.*, Lancet, **336**: 458-461 (1990). These findings were interpreted to indicate that excessive amounts of interstitial collagen may remain after regression of left ventricular hypertrophy. Rossi *et al.*, Am. Heart J., **124**: 700-709 (1992). Rossi *et al.*, *supra*, investigated the effect of captopril on the prevention and

regression of myocardial cell hypertrophy and interstitial fibrosis in pressure overload cardiac hypertrophy, in experimental rats.

Agents that increase cardiac contractility directly (ionotropic agents) were initially thought to benefit patients with heart failure because they improved cardiac output in the short term. However, all positive inotropic agents except digoxigenin have been found to result in increased long-term mortality, in spite of short-term improvements in cardiac performance. Massie, Curr. Op. in Cardiology, 12: 209-217 (1997); Reddy *et al.*, Curr. Opin. Cardiol., 12: 233-241 (1997). Beta-adrenergic receptor blockers have recently been advocated for use in heart failure. Evidence from clinical trials suggests that improvements in cardiac function can be achieved without increased mortality, though documented improvements of patient survival have not yet been demonstrated. See also, U.S. Pat. Nos. 5,935,924, 5,624,806; 5,661,122; and 5,610,134 and WO 95/28173 regarding the use of cardiotropin-1 or antagonists thereof, or growth hormone and/or insulin-like growth factor-I in the treatment of CHF. Another treatment modality is heart transplantation, but this is limited by the availability of donor hearts.

Endothelin is a vasoconstricting peptide comprising 21 amino acids, isolated from swine arterial endothelial culture supernatant and structurally determined. Yanagisawa *et al.*, Nature, 332: 411-415 (1988). Endothelin was later found to exhibit various actions, and endothelin antibodies as endothelin antagonists have proven effective in the treatment of myocardial infarction, renal failure, and other diseases. Since endothelin is present in live bodies and exhibits vasoconstricting action, it is expected to be an endogenous factor involved in the regulation of the circulatory system, and may be associated with hypertension, cardiovascular diseases such as myocardial infarction, and renal diseases such as acute renal failure. Endothelin antagonists are described, for example, in U.S. Pat. No. 5,773,414; JP Pat. Publ. 3130299/1991, EP 457,195; EP 460,679; and EP 552,489. A new endothelin B receptor for identifying endothelin receptor antagonists is described in U.S. Pat. No. 5,773,223.

Current therapy for heart failure is primarily directed to using angiotensin-converting enzyme (ACE) inhibitors, such as captopril, and diuretics. These drugs improve hemodynamic profile and exercise tolerance and reduce the incidence of morbidity and mortality in patients with CHF. Kramer *et al.*, Circulation, 67(4): 807-816 (1983); Captopril Multicenter Research Group, J.A.C.C., 2(4): 755-763 (1983); The CONSENSUS Trial Study Group, N. Engl. J. Med., 316(23): 1429-1435 (1987); The SOLVD Investigators, N. Engl. J. Med., 325(5): 293-302 (1991). Further, they are useful in treating hypertension, left ventricular dysfunction, atherosclerotic vascular disease, and diabetic nephropathy. Brown and Vaughan, *supra*. However, despite proven efficacy, response to ACE inhibitors has been limited. For example, while prolonging survival in the setting of heart failure, ACE inhibitors appear to slow the progression towards end-stage heart failure, and substantial numbers of patients on ACE inhibitors have functional class III heart failure.

Moreover, improvement of functional capacity and exercise time is only small and mortality, although reduced, continues to be high. The CONSENSUS Trial Study Group, N. Engl. J. Med., 316(23): 1429-1453 (1987); The SOLVD Investigators, N. Engl. J. Med., 325(5): 293-302 (1991); Cohn *et al.*, N. Engl. J. Med., 325(5): 303-310 (1991); The Captopril-Digoxin Multicenter Research Group, JAMA, 259(4): 539-544 (1988). Hence, ACE inhibitors consistently appear unable to relieve symptoms in more than 60% of heart failure patients and reduce mortality of heart failure only by approximately 15-20%. For further adverse effects, see Brown and Vaughan,

*supra*.

An alternative to ACE inhibitors is represented by specific AT1 receptor antagonists. Clinical studies are planned to compare the efficacy of these two modalities in the treatment of cardiovascular and renal disease. However, animal model data suggests that the ACE/Ang II pathway, while clearly involved in cardiac hypertrophy, is not the only, or even the primary pathway active in this role. Mouse genetic "knockout" models have been made to test individual components of the pathway. In one such model, the primary cardiac receptor for Ang II, AT sub 1A, has been genetically deleted; these mice do not develop hypertrophy when Ang II is given experimentally (confirming the basic success of the model in eliminating hypertrophy secondary to Ang II). However, when the aorta is constricted in these animals (a model of hypertensive cardiac stress), the hearts still become hypertrophic. This suggests that alternative signaling pathways, not depending on this receptor (AT sub 1A), are activated in hypertension. ACE inhibitors would presumably not be able to inhibit these pathways. *See, Harada et al., Circulation, 97: 1952-1959 (1998). See also, Homcy, Circulation, 97: 1890-1892 (1998) regarding the enigma associated with the process and mechanism of cardiac hypertrophy.*

About 750,000 patients suffer from acute myocardial infarction (AMI) annually, and approximately one-fourth of all deaths in the United States are due to AMI. In recent years, thrombolytic agents, *e.g.*, streptokinase, urokinase, and in particular tissue plasminogen activator (t-PA) have significantly increased the survival of patients who suffered myocardial infarction. When administered as a continuous intravenous infusion over 1.5 to 4 hours, t-PA produces coronary patency at 90 minutes in 69% to 90% of the treated patients. Topol *et al., Am. J. Cardiol., 61: 723-728 (1988); Neuhaus et al., J. Am. Coll. Cardiol., 12: 581-587 (1988); Neuhaus et al., J. Am. Coll. Cardiol., 14: 1566-1569 (1989).* The highest patency rates have been reported with high dose or accelerated dosing regimens. Topol, *J. Am. Coll. Cardiol., 15: 922-924 (1990).* t-PA may also be administered as a single bolus, although due to its relatively short half-life, it is better suited for infusion therapy. Tebbe *et al., Am. J. Cardiol., 64: 448-453 (1989).* A t-PA variant, specifically designed to have longer half-life and very high fibrin specificity, TNK t-PA (a T103N, N117Q, KHRR(296-299)AAAA t-PA variant, Keyt *et al., Proc. Natl. Acad. Sci. USA, 91: 3670-3674 (1994)*) is particularly suitable for bolus administration. However, despite all these advances, the long-term prognosis of patient survival depends greatly on the post-infarction monitoring and treatment of the patients, which should include monitoring and treatment of cardiac hypertrophy.

### 2.3. Growth Factors

Various naturally occurring polypeptides reportedly induce the proliferation of endothelial cells. Among those polypeptides are the basic and acidic fibroblast growth factors (FGF) (Burgess and Maciag, *Annual Rev. Biochem., 58: 575 (1989)*), platelet-derived endothelial cell growth factor (PD-ECGF) (Ishikawa *et al., Nature, 338: 557 (1989)*), and vascular endothelial growth factor (VEGF). Leung *et al., Science, 246: 1306 (1989); Ferrara and Henzel, Biochem. Biophys. Res. Commun., 161: 851 (1989); Tischer et al., Biochem. Biophys. Res. Commun., 165: 1198 (1989); EP 471,754B granted July 31, 1996.*

Media conditioned by cells transfected with the human VEGF (hVEGF) cDNA promoted the proliferation of capillary endothelial cells, whereas control cells did not. Leung *et al., Science, 246: 1306 (1989).* Several

additional cDNAs were identified in human cDNA libraries that encode 121-, 189-, and 206-amino acid isoforms of hVEGF (also collectively referred to as hVEGF-related proteins). The 121-amino acid protein differs from hVEGF by virtue of the deletion of the 44 amino acids between residues 116 and 159 in hVEGF. The 189-amino acid protein differs from hVEGF by virtue of the insertion of 24 amino acids at residue 116 in hVEGF, and apparently is identical to human vascular permeability factor (hVPF). The 206-amino acid protein differs from hVEGF by virtue of an insertion of 41 amino acids at residue 116 in hVEGF. Houck *et al.*, Mol. Endocrin., **5**: 1806 (1991); Ferrara *et al.*, J. Cell. Biochem., **47**: 211 (1991); Ferrara *et al.*, Endocrine Reviews, **13**: 18 (1992); Keck *et al.*, Science, **246**: 1309 (1989); Connolly *et al.*, J. Biol. Chem., **264**: 20017 (1989); EP 370,989 published May 30, 1990.

It is now well established that angiogenesis, which involves the formation of new blood vessels from preexisting endothelium, is implicated in the pathogenesis of a variety of disorders. These include solid tumors and metastasis, atherosclerosis, retrolental fibroplasia, hemangiomas, chronic inflammation, intraocular neovascular syndromes such as proliferative retinopathies, *e.g.*, diabetic retinopathy, age-related macular degeneration (AMD), neovascular glaucoma, immune rejection of transplanted corneal tissue and other tissues, rheumatoid arthritis, and psoriasis. Folkman *et al.*, J. Biol. Chem., **267**: 10931-10934 (1992); Klagsbrun *et al.*, Annu. Rev. Physiol., **53**: 217-239 (1991); and Garner A., "Vascular diseases", In: Pathobiology of Ocular Disease. A Dynamic Approach, Garner A., Klintworth GK, eds., 2nd Edition (Marcel Dekker, NY, 1994), pp 1625-1710.

In the case of tumor growth, angiogenesis appears to be crucial for the transition from hyperplasia to neoplasia, and for providing nourishment for the growth and metastasis of the tumor. Folkman *et al.*, Nature, **339**: 58 (1989). The neovascularization allows the tumor cells to acquire a growth advantage and proliferative autonomy compared to the normal cells. A tumor usually begins as a single aberrant cell which can proliferate only to a size of a few cubic millimeters due to the distance from available capillary beds, and it can stay 'dormant' without further growth and dissemination for a long period of time. Some tumor cells then switch to the angiogenic phenotype to activate endothelial cells, which proliferate and mature into new capillary blood vessels. These newly formed blood vessels not only allow for continued growth of the primary tumor, but also for the dissemination and recolonization of metastatic tumor cells. Accordingly, a correlation has been observed between density of microvessels in tumor sections and patient survival in breast cancer as well as in several other tumors. Weidner *et al.*, N. Engl. J. Med., **324**: 1-6 (1991); Horak *et al.*, Lancet, **340**: 1120-1124 (1992); Macchiarini *et al.*, Lancet, **340**: 145-146 (1992). The precise mechanisms that control the angiogenic switch is not well understood, but it is believed that neovascularization of tumor mass results from the net balance of a multitude of angiogenesis stimulators and inhibitors (Folkman, 1995, Nat Med **1**(1):27-31).

The search for positive regulators of angiogenesis has yielded many candidates, including aFGF, bFGF, TGF- $\alpha$ , TGF- $\beta$ , HGF, TNF- $\alpha$ , angiogenin, IL-8, etc. Folkman *et al.*, J.B.C., *supra*, and Klagsbrun *et al.*, *supra*. The negative regulators so far identified include thrombospondin (Good *et al.*, Proc. Natl. Acad. Sci. USA, **87**: 6624-6628 (1990)), the 16-kilodalton N-terminal fragment of prolactin (Clapp *et al.*, Endocrinology, **133**: 1292-1299 (1993)), angiostatin (O'Reilly *et al.*, Cell, **79**: 315-328 (1994)), and endostatin. O'Reilly *et al.*, Cell, **88**: 277-285 (1996).

Work done over the last several years has established the key role of VEGF, not only in stimulating vascular endothelial cell proliferation, but also in inducing vascular permeability and angiogenesis. Ferrara *et al.*, Endocr. Rev., **18**: 4-25 (1997). The finding that the loss of even a single VEGF allele results in embryonic lethality points to an irreplaceable role played by this factor in the development and differentiation of the vascular system. Furthermore, VEGF has been shown to be a key mediator of neovascularization associated with tumors and intraocular disorders. Ferrara *et al.*, Endocr. Rev., *supra*. The VEGF mRNA is overexpressed by the majority of human tumors examined. Berkman *et al.*, J. Clin. Invest., **91**: 153-159 (1993); Brown *et al.*, Human Pathol., **26**: 86-91 (1995); Brown *et al.*, Cancer Res., **53**: 4727-4735 (1993); Mattern *et al.*, Brit. J. Cancer, **73**: 931-934 (1996); Dvorak *et al.*, Am. J. Pathol., **146**: 1029-1039 (1995).

Also, the concentration levels of VEGF in eye fluids are highly correlated to the presence of active proliferation of blood vessels in patients with diabetic and other ischemia-related retinopathies. Aiello *et al.*, N. Engl. J. Med., **331**: 1480-1487 (1994). Furthermore, recent studies have demonstrated the localization of VEGF in choroidal neovascular membranes in patients affected by AMD. Lopez *et al.*, Invest. Ophthalmol. Vis. Sci., **37**: 855-868 (1996).

Anti-VEGF neutralizing antibodies suppress the growth of a variety of human tumor cell lines in nude mice (Kim *et al.*, Nature, **362**: 841-844 (1993); Warren *et al.*, J. Clin. Invest., **95**: 1789-1797 (1995); Borgström *et al.*, Cancer Res., **56**: 4032-4039 (1996); Melnyk *et al.*, Cancer Res., **56**: 921-924 (1996)) and also inhibit intraocular angiogenesis in models of ischemic retinal disorders. Adamis *et al.*, Arch. Ophthalmol., **114**: 66-71 (1996). Therefore, anti-VEGF monoclonal antibodies or other inhibitors of VEGF action are promising candidates for the treatment of solid tumors and various intraocular neovascular disorders. Such antibodies are described, for example, in EP 817,648 published January 14, 1998 and in WO98/45331 and WO98/45332 both published October 15, 1998.

There exist several other growth factors and mitogens, including transforming oncogenes, that are capable of rapidly inducing a complex set of genes to be expressed by certain cells. Lau and Nathans, Molecular Aspects of Cellular Regulation, **6**: 165-202 (1991). These genes, which have been named immediate-early- or early-response genes, are transcriptionally activated within minutes after contact with a growth factor or mitogen, independent of *de novo* protein synthesis. A group of these intermediate-early genes encodes secreted, extracellular proteins that are needed for coordination of complex biological processes such as differentiation and proliferation, regeneration, and wound healing. Ryseck *et al.*, Cell Growth Differ., **2**: 235-233 (1991).

Highly-related proteins that belong to this group include *cef 10* (Simmons *et al.*, Proc. Natl. Acad. Sci. USA, **86**: 1178-1182 (1989)), *cyr 61*, which is rapidly activated by serum- or platelet-derived growth factor (PDGF) (O'Brien *et al.*, Mol. Cell Biol., **10**: 3569-3577 (1990)), human connective tissue growth factor (CTGF) (Bradham *et al.*, J. Cell. Biol., **114**: 1285-1294 (1991)), which is secreted by human vascular endothelial cells in high levels after activation with transforming growth factor beta (TGF- $\beta$ ), exhibits PDGF-like biological and immunological activities, and competes with PDGF for a particular cell surface receptor, *fisp-12* (Ryseck *et al.*, Cell Growth Differ., **2**: 235-233 (1991)), human vascular IBP-like growth factor (VIGF) (WO 96/17931), and *nov*, normally arrested in adult kidney cells, which was found to be overexpressed in myeloblastosis-associated-virus-type-1-induced nephroblastomas. Joliet *et al.*, Mol. Cell Biol., **12**: 10-21 (1992).

The expression of these immediate-early genes acts as "third messengers" in the cascade of events triggered by growth factors. It is also thought that they are needed to integrate and coordinate complex biological processes, such as differentiation and wound healing in which cell proliferation is a common event.

As additional mitogens, insulin-like growth factor binding proteins (IGFBPs) have been shown, in complex with insulin-like growth factor (IGF), to stimulate increased binding of IGF to fibroblast and smooth muscle cell surface receptors. Clemmons *et al.*, *J. Clin. Invest.*, 77: 1548 (1986). Inhibitory effects of IGFBP on various IGF actions *in vitro* include stimulation of glucose transport by adipocytes, sulfate incorporation by chondrocytes, and thymidine incorporation in fibroblast. Zapf *et al.*, *J. Clin. Invest.*, 63: 1077 (1979). In addition, inhibitory effects of IGFBPs on growth factor-mediated mitogen activity in normal cells have been shown.

#### 2.4. Need for Further Treatments

In view of the role of vascular endothelial cell growth and angiogenesis in many diseases and disorders, it is desirable to have a means of reducing or inhibiting one or more of the biological effects causing these processes. It is also desirable to have a means of assaying for the presence of pathogenic polypeptides in normal and diseased conditions, and especially cancer. Further, in a specific aspect, as there is no generally applicable therapy for the treatment of cardiac hypertrophy, the identification of factors that can prevent or reduce cardiac myocyte hypertrophy is of primary importance in the development of new therapeutic strategies to inhibit pathophysiological cardiac growth. While there are several treatment modalities for various cardiovascular and oncologic disorders, there is still a need for additional therapeutic approaches.

### 3. Summary of the Invention

The present invention provides compositions and methods for modulating (*e.g.*, promoting or inhibiting) angiogenesis and/or cardiovascularization in mammals. The present invention is based on the identification of compounds (*i.e.*, proteins) that test positive in various cardiovascular assays that test modulation (*e.g.*, promotion or inhibition) of certain biological activities. Accordingly, the compounds are believed to be useful drugs and/or drug components for the diagnosis and/or treatment (including prevention and amelioration) of disorders where such effects are desired, such as the promotion or inhibition of angiogenesis, inhibition or stimulation of vascular endothelial cell growth, stimulation of growth or proliferation of vascular endothelial cells, inhibition of tumor growth, inhibition of angiogenesis-dependent tissue growth, stimulation of angiogenesis-dependent tissue growth, inhibition of cardiac hypertrophy and stimulation of cardiac hypertrophy, *e.g.*, for the treatment of congestive heart failure. In addition, the compositions and methods of the invention provide for the diagnostic monitoring of patients undergoing clinical evaluation for the treatment of angiogenesis-related disorders, for monitoring the efficacy of compounds in clinical trials and for identifying subjects who may be predisposed to such angiogenic-related disorders.

In one embodiment, the present invention provides a composition comprising a PRO polypeptide, an agonist or antagonist thereof, or an anti-PRO antibody in admixture with a pharmaceutically acceptable carrier. In one aspect, the composition comprises a therapeutically effective amount of the polypeptide, agonist, antagonist

or antibody. In another aspect, the composition comprises a further active ingredient, namely, a cardiovascular, endothelial or angiogenic agent or an angiostatic agent, preferably an angiogenic or angiostatic agent. Preferably, the composition is sterile. The PRO polypeptide, agonist, antagonist or antibody may be administered in the form of a liquid pharmaceutical formulation, which may be preserved to achieve extended storage stability. Preserved liquid pharmaceutical formulations might contain multiple doses of PRO polypeptide, agonist, antagonist or antibody, and might, therefore, be suitable for repeated use. In a preferred embodiment, where the composition comprises an antibody, the antibody is a monoclonal antibody, an antibody fragment, a humanized antibody, or a single-chain antibody.

In a further embodiment, the present invention provides a method for preparing such a composition useful for the treatment of a cardiovascular, endothelial or angiogenic disorder comprising admixing a therapeutically effective amount of a PRO polypeptide, agonist, antagonist or antibody with a pharmaceutically acceptable carrier.

In a still further aspect, the present invention provides an article of manufacture comprising:

- (a) a composition of matter comprising a PRO polypeptide or agonist or antagonist thereof;
- (b) a container containing said composition; and
- (c) a label affixed to said container, or a package insert included in said container referring to the use of said PRO polypeptide or agonist or antagonist thereof in the treatment of a cardiovascular, endothelial or angiogenic disorder, wherein the agonist or antagonist may be an antibody which binds to the PRO polypeptide. The composition may comprise a therapeutically effective amount of the PRO polypeptide or the agonist or antagonist thereof.

In another embodiment, the present invention provides a method for identifying an agonist of a PRO polypeptide comprising:

- (a) contacting cells and a test compound to be screened under conditions suitable for the induction of a cellular response normally induced by a PRO polypeptide; and
- (b) determining the induction of said cellular response to determine if the test compound is an effective agonist, wherein the induction of said cellular response is indicative of said test compound being an effective agonist.

In another embodiment, the present invention provides a method for identifying an agonist of a PRO polypeptide comprising:

- (a) contacting cells and a test compound to be screened under conditions suitable for the stimulation of cell proliferation by a PRO polypeptide; and
- (b) measuring the proliferation of said cells to determine if the test compound is an effective agonist, wherein the stimulation of cell proliferation is indicative of said test compound being an effective agonist.

In another embodiment, the invention provides a method for identifying a compound that inhibits the activity of a PRO polypeptide comprising contacting a test compound with a PRO polypeptide under conditions and for a time sufficient to allow the test compound and polypeptide to interact and determining whether the activity of the PRO polypeptide is inhibited. In a specific preferred aspect, either the test compound or the PRO polypeptide is immobilized on a solid support. In another preferred aspect, the non-immobilized component carries a detectable

label. In a preferred aspect, this method comprises the steps of:

(a) contacting cells and a test compound to be screened in the presence of a PRO polypeptide under conditions suitable for the induction of a cellular response normally induced by a PRO polypeptide; and

5 (b) determining the induction of said cellular response to determine if the test compound is an effective antagonist.

In another preferred aspect, this process comprises the steps of:

(a) contacting cells and a test compound to be screened in the presence of a PRO polypeptide under conditions suitable for the stimulation of cell proliferation by a PRO polypeptide; and

(b) measuring the proliferation of the cells to determine if the test compound is an effective antagonist.

10 In another embodiment, the invention provides a method for identifying a compound that inhibits the expression of a PRO polypeptide in cells that normally expresses the polypeptide, wherein the method comprises contacting the cells with a test compound and determining whether the expression of the PRO polypeptide is inhibited. In a preferred aspect, this method comprises the steps of:

15 (a) contacting cells and a test compound to be screened under conditions suitable for allowing expression of the PRO polypeptide; and

(b) determining the inhibition of expression of said polypeptide.

In a still further embodiment, the invention provides a compound that inhibits the expression of a PRO polypeptide, such as a compound that is identified by the methods set forth above.

20 Another aspect of the present invention is directed to an agonist or an antagonist of a PRO polypeptide which may optionally be identified by the methods described above.

One type of antagonist of a PRO polypeptide that inhibits one or more of the functions or activities of the PRO polypeptide is an antibody. Hence, in another aspect, the invention provides an isolated antibody that binds a PRO polypeptide. In a preferred aspect, the antibody is a monoclonal antibody, which preferably has non-human complementarity-determining-region (CDR) residues and human framework-region (FR) residues. The antibody  
25 may be labeled and may be immobilized on a solid support. In a further aspect, the antibody is an antibody fragment, a single-chain antibody, or a humanized antibody. Preferably, the antibody specifically binds to the polypeptide.

30 In a still further aspect, the present invention provides a method for diagnosing a disease or susceptibility to a disease which is related to a mutation in a PRO polypeptide-encoding nucleic acid sequence comprising determining the presence or absence of said mutation in the PRO polypeptide nucleic acid sequence, wherein the presence or absence of said mutation is indicative of the presence of said disease or susceptibility to said disease.

35 In a still further aspect, the invention provides a method of diagnosing a cardiovascular, endothelial or angiogenic disorder in a mammal which comprises analyzing the level of expression of a gene encoding a PRO polypeptide (a) in a test sample of tissue cells obtained from said mammal, and (b) in a control sample of known normal tissue cells of the same cell type, wherein a higher or lower expression level in the test sample as compared to the control sample is indicative of the presence of a cardiovascular, endothelial or angiogenic disorder in said mammal. The expression of a gene encoding a PRO polypeptide may optionally be accomplished by measuring



the level of mRNA or the polypeptide in the test sample as compared to the control sample.

In a still further aspect, the present invention provides a method of diagnosing a cardiovascular, endothelial or angiogenic disorder in a mammal which comprises detecting the presence or absence of a PRO polypeptide in a test sample of tissue cells obtained from said mammal, wherein the presence or absence of said PRO polypeptide in said test sample is indicative of the presence of a cardiovascular, endothelial or angiogenic disorder in said mammal.

In a still further embodiment, the invention provides a method of diagnosing a cardiovascular, endothelial or angiogenic disorder in a mammal comprising (a) contacting an anti-PRO antibody with a test sample of tissue cells obtained from the mammal, and (b) detecting the formation of a complex between the antibody and the PRO polypeptide in the test sample, wherein the formation of said complex is indicative of the presence of a cardiovascular, endothelial or angiogenic disorder in the mammal. The detection may be qualitative or quantitative, and may be performed in comparison with monitoring the complex formation in a control sample of known normal tissue cells of the same cell type. A larger or smaller quantity of complexes formed in the test sample indicates the presence of a cardiovascular, endothelial or angiogenic dysfunction in the mammal from which the test tissue cells were obtained. The antibody preferably carries a detectable label. Complex formation can be monitored, for example, by light microscopy, flow cytometry, fluorimetry, or other techniques known in the art. The test sample is usually obtained from an individual suspected to have a cardiovascular, endothelial or angiogenic disorder.

In another embodiment, the invention provides a method for determining the presence of a PRO polypeptide in a sample comprising exposing a sample suspected of containing the PRO polypeptide to an anti-PRO antibody and determining binding of said antibody to a component of said sample. In a specific aspect, the sample comprises a cell suspected of containing the PRO polypeptide and the antibody binds to the cell. The antibody is preferably detectably labeled and/or bound to a solid support.

In further aspects, the invention provides a cardiovascular, endothelial or angiogenic disorder diagnostic kit comprising an anti-PRO antibody and a carrier in suitable packaging. Preferably, such kit further comprises instructions for using said antibody to detect the presence of the PRO polypeptide. Preferably, the carrier is a buffer, for example. Preferably, the cardiovascular, endothelial or angiogenic disorder is cancer.

In yet another embodiment, the present invention provides a method for treating a cardiovascular, endothelial or angiogenic disorder in a mammal comprising administering to the mammal an effective amount of a PRO polypeptide. Preferably, the disorder is cardiac hypertrophy, trauma such as wounds or burns, or a type of cancer. In a further aspect, the mammal is further exposed to angioplasty or a drug that treats cardiovascular, endothelial or angiogenic disorders such as ACE inhibitors or chemotherapeutic agents if the cardiovascular, endothelial or angiogenic disorder is a type of cancer. Preferably, the mammal is human, preferably one who is at risk of developing cardiac hypertrophy and more preferably has suffered myocardial infarction.

In another preferred aspect, the cardiac hypertrophy is characterized by the presence of an elevated level of PGF<sub>2α</sub>. Alternatively, the cardiac hypertrophy may be induced by myocardial infarction, wherein preferably the administration of the PRO polypeptide is initiated within 48 hours, more preferably within 24 hours, following myocardial infarction.

In another preferred embodiment, the cardiovascular, endothelial or angiogenic disorder is cardiac hypertrophy and said PRO polypeptide is administered together with a cardiovascular, endothelial or angiogenic agent. The preferred cardiovascular, endothelial or angiogenic agent for this purpose is selected from the group consisting of an antihypertensive drug, an ACE inhibitor, an endothelin receptor antagonist and a thrombolytic agent. If a thrombolytic agent is administered, preferably the PRO polypeptide is administered following administration of such agent. More preferably, the thrombolytic agent is recombinant human tissue plasminogen activator.

In another preferred aspect, the cardiovascular, endothelial or angiogenic disorder is cardiac hypertrophy and the PRO polypeptide is administered following primary angioplasty for the treatment of acute myocardial infarction, preferably wherein the mammal is further exposed to angioplasty or a cardiovascular, endothelial, or angiogenic agent.

In another preferred embodiment, the cardiovascular, endothelial or angiogenic disorder is a cancer and the PRO polypeptide is administered in combination with a chemotherapeutic agent, a growth inhibitory agent or a cytotoxic agent.

In a further embodiment, the invention provides a method for treating a cardiovascular, endothelial or angiogenic disorder in a mammal comprising administering to the mammal an effective amount of a PRO polypeptide agonist, antagonist or anti-PRO antibody. Preferably, the cardiovascular, endothelial or angiogenic disorder is cardiac hypertrophy, trauma, a cancer, or age-related macular degeneration. Also preferred is where the mammal is human, and where an effective amount of an angiogenic or angiostatic agent is administered in conjunction with the agonist, antagonist or anti-PRO antibody.

In still further embodiments, the invention provides a method for treating a cardiovascular, endothelial or angiogenic disorder in a mammal that suffers therefrom comprising administering to the mammal a nucleic acid molecule that codes for either (a) a PRO polypeptide, (b) an agonist of a PRO polypeptide or (c) an antagonist of a PRO polypeptide, wherein said agonist or antagonist may be an anti-PRO antibody. In a preferred embodiment, the mammal is human. In another preferred embodiment, the gene is administered via *ex vivo* gene therapy. In a further preferred embodiment, the gene is comprised within a vector, more preferably an adenoviral, adeno-associated viral, lentiviral, or retroviral vector.

In yet another aspect, the invention provides a recombinant retroviral particle comprising a retroviral vector consisting essentially of a promoter, nucleic acid encoding (a) a PRO polypeptide, (b) an agonist polypeptide of a PRO polypeptide, or (c) an antagonist polypeptide of a PRO polypeptide, and a signal sequence for cellular secretion of the polypeptide, wherein the retroviral vector is in association with retroviral structural proteins. Preferably, the signal sequence is from a mammal, such as from a native PRO polypeptide.

In a still further embodiment, the invention supplies an *ex vivo* producer cell comprising a nucleic acid construct that expresses retroviral structural proteins and also comprises a retroviral vector consisting essentially of a promoter, nucleic acid encoding (a) a PRO polypeptide, (b) an agonist polypeptide of a PRO polypeptide or (c) an antagonist polypeptide of a PRO polypeptide, and a signal sequence for cellular secretion of the polypeptide, wherein said producer cell packages the retroviral vector in association with the structural proteins to produce

recombinant retroviral particles.

5 In yet another embodiment, the invention provides a method for inhibiting endothelial cell growth in a mammal comprising administering to the mammal (a) a PRO polypeptide, (b) an agonist of a PRO polypeptide, or (c) an antagonist of a PRO polypeptide, wherein endothelial cell growth in said mammal is inhibited, and wherein said agonist or antagonist may be an anti-PRO antibody. Preferably, the mammal is human and the endothelial cell growth is associated with a tumor or a retinal disorder.

10 In yet another embodiment, the invention provides a method for stimulating endothelial cell growth in a mammal comprising administering to the mammal (a) a PRO polypeptide, (b) an agonist of a PRO polypeptide, or (c) an antagonist of a PRO polypeptide, wherein endothelial cell growth in said mammal is stimulated, and wherein said agonist or antagonist may be an anti-PRO antibody. Preferably, the mammal is human.

15 In yet another embodiment, the invention provides a method for inhibiting cardiac hypertrophy in a mammal comprising administering to the mammal (a) a PRO polypeptide, (b) an agonist of a PRO polypeptide, or (c) an antagonist of a PRO polypeptide, wherein cardiac hypertrophy in said mammal is inhibited, and wherein said agonist or antagonist may be an anti-PRO antibody. Preferably, the mammal is human and the cardiac hypertrophy has been induced by myocardial infarction.

20 In yet another embodiment, the invention provides a method for stimulating cardiac hypertrophy in a mammal comprising administering to the mammal (a) a PRO polypeptide, (b) an agonist of a PRO polypeptide, or (c) an antagonist of a PRO polypeptide, wherein cardiac hypertrophy in said mammal is stimulated, and wherein said agonist or antagonist may be an anti-PRO antibody. Preferably, the mammal is human who suffers from congestive heart failure.

25 In yet another embodiment, the invention provides a method for inhibiting angiogenesis induced by a PRO polypeptide in a mammal comprising administering a therapeutically effective amount of an anti-PRO antibody to the mammal. Preferably, the mammal is a human, and more preferably the mammal has a tumor or a retinal disorder.

30 In yet another embodiment, the invention provides a method for stimulating angiogenesis induced by a PRO polypeptide in a mammal comprising administering a therapeutically effective amount of a PRO polypeptide to the mammal. Preferably, the mammal is a human, and more preferably angiogenesis would promote tissue regeneration or wound healing.

35 In yet another embodiment, the invention provides a method for modulating (e.g., inhibiting or stimulating) endothelial cell growth in a mammal comprising administering to the mammal a PRO21, PRO181, PRO205, PRO214, PRO221, PRO229, PRO231, PRO238, PRO241, PRO247, PRO256, PRO258, PRO263, PRO265, PRO295, PRO321, PRO322, PRO337, PRO363, PRO365, PRO444, PRO533, PRO697, PRO720, PRO725, PRO771, PRO788, PRO791, PRO819, PRO827, PRO828, PRO836, PRO846, PRO865, PRO1005, PRO1006, PRO1007, PRO1025, PRO1029, PRO1054, PRO1071, PRO1075, PRO1079, PRO1080, PRO1114, PRO1131, PRO1155, PRO1160, PRO1184, PRO1186, PRO1190, PRO1192, PRO1195, PRO1244, PRO1272, PRO1273, PRO1274, PRO1279, PRO1283, PRO1286, PRO1306, PRO1309, PRO1325, PRO1329, PRO1347, PRO1356, PRO1376, PRO1382, PRO1411, PRO1412, PRO1419, PRO1474, PRO1477, PRO1488, PRO1508, PRO1550,

PRO1556, PRO1760, PRO1782, PRO1787, PRO1801, PRO1868, PRO1887, PRO1890, PRO3438, PRO3444, PRO4302, PRO4324, PRO4333, PRO4341, PRO4342, PRO4353, PRO4354, PRO4356, PRO4371, PRO4405, PRO4408, PRO4422, PRO4425, PRO4499, PRO5723, PRO5725, PRO5737, PRO5776, PRO6006, PRO6029, PRO6071, PRO7436, PRO9771, PRO9821, PRO9873, PRO10008, PRO10096, PRO19670, PRO20040, PRO20044, PRO21055, PRO21384 or PRO28631 polypeptide, agonist or antagonist thereof, wherein endothelial cell growth in said mammal is modulated.

In yet another embodiment, the invention provides a method for modulating (*e.g.*, inhibiting or stimulating) smooth muscle cell growth in a mammal comprising administering to the mammal a PRO162, PRO181, PRO182, PRO195, PRO204, PRO221, PRO230, PRO256, PRO258, PRO533, PRO697, PRO725, PRO738, PRO826, PRO836, PRO840, PRO846, PRO865, PRO982, PRO1025, PRO1029, PRO1071, PRO1080, PRO1083, PRO1134, PRO1160, PRO1182, PRO1184, PRO1186, PRO1192, PRO1265, PRO1274, PRO1279, PRO1283, PRO1306, PRO1308, PRO1309, PRO1325, PRO1337, PRO1338, PRO1343, PRO1376, PRO1387, PRO1411, PRO1412, PRO1415, PRO1434, PRO1474, PRO1488, PRO1550, PRO1556, PRO1567, PRO1600, PRO1754, PRO1758, PRO1760, PRO1787, PRO1865, PRO1868, PRO1917, PRO1928, PRO3438, PRO3562, PRO4302, PRO4333, PRO4345, PRO4353, PRO4354, PRO4405, PRO4408, PRO4430, PRO4503, PRO5725, PRO6714, PRO9771, PRO9820, PRO9940, PRO10096, PRO21055, PRO21184 or PRO21366 polypeptide, agonist or antagonist thereof, wherein endothelial cell growth in said mammal is modulated.

In yet another embodiment, the invention provides a method for modulating (*e.g.*, inducing or reducing) cardiac hypertrophy in a mammal comprising administering to the mammal a PRO21 polypeptide, agonist or antagonist thereof, wherein cardiac hypertrophy in said mammal is modulated.

In yet another embodiment, the invention provides a method for modulating (*e.g.*, inducing or reducing) endothelial cell apoptosis in a mammal comprising administering to the mammal a PRO4302 polypeptide, agonist or antagonist thereof, wherein cardiac hypertrophy in said mammal is modulated.

In yet another embodiment, the invention provides a method for modulating (*e.g.*, stimulating or inhibiting) angiogenesis in a mammal comprising administering a therapeutically effective amount of a PRO1376 or PRO1449 polypeptide, agonist or antagonist thereof to the mammal, wherein said angiogenesis is modulated.

In yet another embodiment, the invention provides a method for modulating (*e.g.*, inducing or reducing) angiogenesis by modulating (*e.g.*, inducing or reducing) endothelial cell tube formation in a mammal comprising administering to the mammal a PRO178, PRO195, PRO228, PRO301, PRO302, PRO532, PRO724, PRO730, PRO734, PRO793, PRO871, PRO938, PRO1012, PRO1120, PRO1139, PRO1198, PRO1287, PRO1361, PRO1864, PRO1873, PRO2010, PRO3579, PRO4313, PRO4527, PRO4538, PRO4553, PRO4995, PRO5730, PRO6008, PRO7223, PRO7248 or PRO7261 polypeptide, agonist or antagonist thereof, wherein endothelial cell tube formation in said mammal is modulated.

In other embodiments of the present invention, the invention provides an isolated nucleic acid molecule comprising a nucleotide sequence that encodes a PRO polypeptide.

In one aspect, the isolated nucleic acid molecule comprises a nucleotide sequence having at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97% or 98%

nucleic acid sequence identity and alternatively at least about 99% nucleic acid sequence identity to (a) a DNA molecule encoding a PRO polypeptide having a full-length amino acid sequence as disclosed herein, an amino acid sequence lacking the signal peptide as disclosed herein, an extracellular domain of a transmembrane protein, with or without the signal peptide, as disclosed herein or any other specifically defined fragment of the full-length amino acid sequence as disclosed herein, or (b) the complement of the DNA molecule of (a).

In other aspects, the isolated nucleic acid molecule comprises a nucleotide sequence having at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97% or 98% nucleic acid sequence identity and alternatively at least about 99% nucleic acid sequence identity to (a) a DNA molecule comprising the coding sequence of a full-length PRO polypeptide cDNA as disclosed herein, the coding sequence of a PRO polypeptide lacking the signal peptide as disclosed herein, the coding sequence of an extracellular domain of a transmembrane PRO polypeptide, with or without the signal peptide, as disclosed herein or the coding sequence of any other specifically defined fragment of the full-length amino acid sequence as disclosed herein, or (b) the complement of the DNA molecule of (a).

In a further aspect, the invention provides an isolated nucleic acid molecule comprising a nucleotide sequence having at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97% or 98% nucleic acid sequence identity and alternatively at least about 99% nucleic acid sequence identity to (a) a DNA molecule that encodes the same mature polypeptide encoded by any of the human protein cDNAs deposited with the ATCC as disclosed herein, or (b) the complement of the DNA molecule of (a).

Another aspect of the present invention provides an isolated nucleic acid molecule comprising a nucleotide sequence encoding a PRO polypeptide which is either transmembrane domain-deleted or transmembrane domain-inactivated, or is complementary to such encoding nucleotide sequence, wherein the transmembrane domain(s) of such polypeptide are disclosed herein. Therefore, soluble extracellular domains of the herein described PRO polypeptides are contemplated.

Another embodiment is directed to fragments of a PRO polypeptide coding sequence, or the complement thereof, that may find use as, for example, hybridization probes, for encoding fragments of a PRO polypeptide that may optionally encode a polypeptide comprising a binding site for an anti-PRO antibody or as antisense oligonucleotide probes. Such nucleic acid fragments are usually at least about 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 250, 300, 350, 400, 450, 500, 600, 700 or 800 nucleotides in length and alternatively at least about 1000 nucleotides in length, wherein in this context the term "about" means the referenced nucleotide sequence length plus or minus 10% of that referenced length. It is noted that novel fragments of a PRO polypeptide-encoding nucleotide sequence may be determined in a routine manner by aligning the PRO polypeptide-encoding nucleotide sequence with other known nucleotide sequences using any of a number of well known sequence alignment programs and determining which PRO polypeptide-encoding nucleotide sequence fragment(s) are novel. All of such PRO polypeptide-encoding nucleotide sequences are contemplated herein. Also contemplated are the PRO polypeptide fragments encoded by these nucleotide molecule fragments, preferably those PRO polypeptide fragments that comprise a binding site for an anti-PRO antibody.

In another embodiment, the invention provides an isolated PRO polypeptide encoded by any of the isolated

nucleic acid sequences hereinabove identified.

5 In a certain aspect, the invention provides an isolated PRO polypeptide comprising an amino acid sequence having at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97% or 98% amino acid sequence identity and alternatively at least about 99% amino acid sequence identity to a PRO polypeptide having a full-length amino acid sequence as disclosed herein, an amino acid sequence lacking the signal peptide as disclosed herein, an extracellular domain of a transmembrane protein, with or without the signal peptide, as disclosed herein or any other specifically defined fragment of the full-length amino acid sequence as disclosed herein.

10 In a further aspect, the invention provides an isolated PRO polypeptide comprising an amino acid sequence having at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97% or 98% amino acid sequence identity and alternatively at least about 99% amino acid sequence identity to an amino acid sequence encoded by any of the human protein cDNAs deposited with the ATCC as disclosed herein.

15 In a specific aspect, the invention provides an isolated PRO polypeptide without the N-terminal signal sequence and/or the initiating methionine and that is encoded by a nucleotide sequence that encodes such an amino acid sequence as hereinbefore described. Processes for producing the same are also herein described, wherein those processes comprise culturing a host cell comprising a vector which comprises the appropriate encoding nucleic acid molecule under conditions suitable for expression of the PRO polypeptide and recovering the PRO polypeptide from the cell culture.

20 Another aspect of the invention provides an isolated PRO polypeptide which is either transmembrane domain-deleted or transmembrane domain-inactivated. Processes for producing the same are also herein described, wherein those processes comprise culturing a host cell comprising a vector which comprises the appropriate encoding nucleic acid molecule under conditions suitable for expression of the PRO polypeptide and recovering the PRO polypeptide from the cell culture.

25 In yet another embodiment, the invention provides agonists and antagonists of a native PRO polypeptide as defined herein. In a particular embodiment, the agonist or antagonist is an anti-PRO antibody or a small molecule.

30 In a further embodiment, the invention provides a method of identifying agonists or antagonists to a PRO polypeptide which comprise contacting the PRO polypeptide with a candidate molecule and monitoring a biological activity mediated by said PRO polypeptide. Preferably, the PRO polypeptide is a native PRO polypeptide.

In a still further embodiment, the invention provides a composition of matter comprising a PRO polypeptide, or an agonist or antagonist of a PRO polypeptide as herein described, or an anti-PRO antibody, in combination with a carrier. Optionally, the carrier is a pharmaceutically acceptable carrier.

35 Another embodiment of the present invention is directed to the use of a PRO polypeptide, or an agonist or antagonist thereof as hereinbefore described, or an anti-PRO antibody, for the preparation of a medicament useful in the treatment of a condition which is responsive to the PRO polypeptide, an agonist or antagonist thereof or an anti-PRO antibody.

In additional embodiments of the present invention, the invention provides vectors comprising DNA encoding any of the herein described polypeptides. Host cells comprising any such vector are also provided. By way of example, the host cells may be CHO cells, *E. coli*, yeast, or Baculovirus-infected insect cells. A process for producing any of the herein described polypeptides is further provided and comprises culturing host cells under conditions suitable for expression of the desired polypeptide and recovering the desired polypeptide from the cell culture.

In other embodiments, the invention provides chimeric molecules comprising any of the herein described polypeptides fused to a heterologous polypeptide or amino acid sequence. Example of such chimeric molecules comprise any of the herein described polypeptides fused to an epitope tag sequence or a Fc region of an immunoglobulin.

In yet another embodiment, the invention provides an antibody which specifically binds to any of the above or below described polypeptides. Optionally, the antibody is a monoclonal antibody, humanized antibody, antibody fragment or single-chain antibody.

In yet other embodiments, the invention provides oligonucleotide probes useful for isolating genomic and cDNA nucleotide sequences or as antisense probes, wherein those probes may be derived from any of the above or below described nucleotide sequences.

#### 4. Brief Description of the Drawings

Figure 1 shows a nucleotide sequence (SEQ ID NO:1) of a native sequence PRO181 cDNA, wherein SEQ ID NO:1 is a clone designated herein as "DNA23330-1390".

Figure 2 shows the amino acid sequence (SEQ ID NO:2) derived from the coding sequence of SEQ ID NO:1 shown in Figure 1.

Figure 3 shows a nucleotide sequence (SEQ ID NO:3) of a native sequence PRO178 cDNA, wherein SEQ ID NO:3 is a clone designated herein as "DNA23339-1130".

Figure 4 shows the amino acid sequence (SEQ ID NO:4) derived from the coding sequence of SEQ ID NO:3 shown in Figure 3.

Figure 5 shows a nucleotide sequence (SEQ ID NO:5) of a native sequence PRO444 cDNA, wherein SEQ ID NO:5 is a clone designated herein as "DNA26846-1397".

Figure 6 shows the amino acid sequence (SEQ ID NO:6) derived from the coding sequence of SEQ ID NO:5 shown in Figure 5.

Figure 7 shows a nucleotide sequence (SEQ ID NO:7) of a native sequence PRO195 cDNA, wherein SEQ ID NO:7 is a clone designated herein as "DNA26847-1395".

Figure 8 shows the amino acid sequence (SEQ ID NO:8) derived from the coding sequence of SEQ ID NO:7 shown in Figure 7.

Figure 9 shows a nucleotide sequence (SEQ ID NO:9) of a native sequence PRO182 cDNA, wherein SEQ ID NO:9 is a clone designated herein as "DNA27865-1091".

Figure 10 shows the amino acid sequence (SEQ ID NO:10) derived from the coding sequence of SEQ ID

NO:9 shown in Figure 9.

Figure 11 shows a nucleotide sequence (SEQ ID NO:11) of a native sequence PRO205 cDNA, wherein SEQ ID NO:11 is a clone designated herein as "DNA30868-1156".

5 Figure 12 shows the amino acid sequence (SEQ ID NO:12) derived from the coding sequence of SEQ ID NO:11 shown in Figure 11.

Figure 13 shows a nucleotide sequence (SEQ ID NO:13) of a native sequence PRO204 cDNA, wherein SEQ ID NO:13 is a clone designated herein as "DNA30871-1157".

Figure 14 shows the amino acid sequence (SEQ ID NO:14) derived from the coding sequence of SEQ ID NO:13 shown in Figure 13.

10 Figure 15 shows a nucleotide sequence (SEQ ID NO:15) of a native sequence PRO1873 cDNA, wherein SEQ ID NO:15 is a clone designated herein as "DNA30880".

Figure 16 shows the amino acid sequence (SEQ ID NO:16) derived from the coding sequence of SEQ ID NO:15 shown in Figure 15.

15 Figure 17 shows a nucleotide sequence (SEQ ID NO:17) of a native sequence PRO214 cDNA, wherein SEQ ID NO:17 is a clone designated herein as "DNA32286-1191".

Figure 18 shows the amino acid sequence (SEQ ID NO:18) derived from the coding sequence of SEQ ID NO:17 shown in Figure 17.

Figure 19 shows a nucleotide sequence (SEQ ID NO:19) of a native sequence PRO221 cDNA, wherein SEQ ID NO:19 is a clone designated herein as "DNA33089-1132".

20 Figure 20 shows the amino acid sequence (SEQ ID NO:20) derived from the coding sequence of SEQ ID NO:19 shown in Figure 19.

Figure 21 shows a nucleotide sequence (SEQ ID NO:21) of a native sequence PRO228 cDNA, wherein SEQ ID NO:21 is a clone designated herein as "DNA33092-1202".

25 Figure 22 shows the amino acid sequence (SEQ ID NO:22) derived from the coding sequence of SEQ ID NO:21 shown in Figure 21.

Figure 23 shows a nucleotide sequence (SEQ ID NO:23) of a native sequence PRO229 cDNA, wherein SEQ ID NO:23 is a clone designated herein as "DNA33100-1159".

Figure 24 shows the amino acid sequence (SEQ ID NO:24) derived from the coding sequence of SEQ ID NO:23 shown in Figure 23.

30 Figure 25 shows a nucleotide sequence (SEQ ID NO:25) of a native sequence PRO230 cDNA, wherein SEQ ID NO:25 is a clone designated herein as "DNA33223-1136".

Figure 26 shows the amino acid sequence (SEQ ID NO:26) derived from the coding sequence of SEQ ID NO:25 shown in Figure 25.

35 Figure 27 shows a nucleotide sequence (SEQ ID NO:27) of a native sequence PRO7223 cDNA, wherein SEQ ID NO:27 is a clone designated herein as "DNA34385".

Figure 28 shows the amino acid sequence (SEQ ID NO:28) derived from the coding sequence of SEQ ID NO:27 shown in Figure 27.



Figure 29 shows a nucleotide sequence (SEQ ID NO:29) of a native sequence PRO241 cDNA, wherein SEQ ID NO:29 is a clone designated herein as "DNA34392-1170".

Figure 30 shows the amino acid sequence (SEQ ID NO:30) derived from the coding sequence of SEQ ID NO:29 shown in Figure 29.

5        Figure 31 shows a nucleotide sequence (SEQ ID NO:31) of a native sequence PRO263 cDNA, wherein SEQ ID NO:31 is a clone designated herein as "DNA34431-1177".

Figure 32 shows the amino acid sequence (SEQ ID NO:32) derived from the coding sequence of SEQ ID NO:31 shown in Figure 31.

10       Figure 33 shows a nucleotide sequence (SEQ ID NO:33) of a native sequence PRO321 cDNA, wherein SEQ ID NO:33 is a clone designated herein as "DNA34433-1308".

Figure 34 shows the amino acid sequence (SEQ ID NO:34) derived from the coding sequence of SEQ ID NO:33 shown in Figure 33.

Figure 35 shows a nucleotide sequence (SEQ ID NO:35) of a native sequence PRO231 cDNA, wherein SEQ ID NO:35 is a clone designated herein as "DNA34434-1139".

15       Figure 36 shows the amino acid sequence (SEQ ID NO:36) derived from the coding sequence of SEQ ID NO:35 shown in Figure 35.

Figure 37 shows a nucleotide sequence (SEQ ID NO:37) of a native sequence PRO238 cDNA, wherein SEQ ID NO:37 is a clone designated herein as "DNA35600-1162".

20       Figure 38 shows the amino acid sequence (SEQ ID NO:38) derived from the coding sequence of SEQ ID NO:37 shown in Figure 37.

Figure 39 shows a nucleotide sequence (SEQ ID NO:39) of a native sequence PRO247 cDNA, wherein SEQ ID NO:39 is a clone designated herein as "DNA35673-1201".

Figure 40 shows the amino acid sequence (SEQ ID NO:40) derived from the coding sequence of SEQ ID NO:39 shown in Figure 39.

25       Figure 41 shows a nucleotide sequence (SEQ ID NO:41) of a native sequence PRO256 cDNA, wherein SEQ ID NO:41 is a clone designated herein as "DNA35880-1160".

Figure 42 shows the amino acid sequence (SEQ ID NO:42) derived from the coding sequence of SEQ ID NO:41 shown in Figure 41.

30       Figure 43 shows a nucleotide sequence (SEQ ID NO:43) of a native sequence PRO258 cDNA, wherein SEQ ID NO:43 is a clone designated herein as "DNA35918-1174".

Figure 44 shows the amino acid sequence (SEQ ID NO:44) derived from the coding sequence of SEQ ID NO:43 shown in Figure 43.

Figure 45 shows a nucleotide sequence (SEQ ID NO:45) of a native sequence PRO265 cDNA, wherein SEQ ID NO:45 is a clone designated herein as "DNA36350-1158".

35       Figure 46 shows the amino acid sequence (SEQ ID NO:46) derived from the coding sequence of SEQ ID NO:45 shown in Figure 45.

Figure 47 shows a nucleotide sequence (SEQ ID NO:47) of a native sequence PRO21 cDNA, wherein SEQ

ID NO:47 is a clone designated herein as "DNA36638-1056".

Figure 48 shows the amino acid sequence (SEQ ID NO:48) derived from the coding sequence of SEQ ID NO:47 shown in Figure 47.

5 Figure 49 shows a nucleotide sequence (SEQ ID NO:49) of a native sequence PRO295 cDNA, wherein SEQ ID NO:49 is a clone designated herein as "DNA38268-1188".

Figure 50 shows the amino acid sequence (SEQ ID NO:50) derived from the coding sequence of SEQ ID NO:49 shown in Figure 49.

Figure 51 shows a nucleotide sequence (SEQ ID NO:51) of a native sequence PRO302 cDNA, wherein SEQ ID NO:51 is a clone designated herein as "DNA40370-1217".

10 Figure 52 shows the amino acid sequence (SEQ ID NO:52) derived from the coding sequence of SEQ ID NO:51 shown in Figure 51.

Figure 53 shows a nucleotide sequence (SEQ ID NO:53) of a native sequence PRO301 cDNA, wherein SEQ ID NO:53 is a clone designated herein as "DNA40628-1216".

15 Figure 54 shows the amino acid sequence (SEQ ID NO:54) derived from the coding sequence of SEQ ID NO:53 shown in Figure 53.

Figure 55 shows a nucleotide sequence (SEQ ID NO:55) of a native sequence PRO337 cDNA, wherein SEQ ID NO:55 is a clone designated herein as "DNA43316-1237".

Figure 56 shows the amino acid sequence (SEQ ID NO:56) derived from the coding sequence of SEQ ID NO:55 shown in Figure 55.

20 Figure 57 shows a nucleotide sequence (SEQ ID NO:57) of a native sequence PRO7248 cDNA, wherein SEQ ID NO:57 is a clone designated herein as "DNA44195".

Figure 58 shows the amino acid sequence (SEQ ID NO:58) derived from the coding sequence of SEQ ID NO:57 shown in Figure 57.

25 Figure 59 shows a nucleotide sequence (SEQ ID NO:59) of a native sequence PRO846 cDNA, wherein SEQ ID NO:59 is a clone designated herein as "DNA44196-1353".

Figure 60 shows the amino acid sequence (SEQ ID NO:60) derived from the coding sequence of SEQ ID NO:59 shown in Figure 59.

Figure 61 shows a nucleotide sequence (SEQ ID NO:61) of a native sequence PRO1864 cDNA, wherein SEQ ID NO:61 is a clone designated herein as "DNA45409-2511".

30 Figure 62 shows the amino acid sequence (SEQ ID NO:62) derived from the coding sequence of SEQ ID NO:61 shown in Figure 61.

Figure 63 shows a nucleotide sequence (SEQ ID NO:63) of a native sequence PRO363 cDNA, wherein SEQ ID NO:63 is a clone designated herein as "DNA45419-1252".

35 Figure 64 shows the amino acid sequence (SEQ ID NO:64) derived from the coding sequence of SEQ ID NO:63 shown in Figure 63.

Figure 65 shows a nucleotide sequence (SEQ ID NO:65) of a native sequence PRO730 cDNA, wherein SEQ ID NO:65 is a clone designated herein as "DNA45624-1400".

Figure 66 shows the amino acid sequence (SEQ ID NO:66) derived from the coding sequence of SEQ ID NO:65 shown in Figure 65.

Figure 67 shows a nucleotide sequence (SEQ ID NO:67) of a native sequence PRO365 cDNA, wherein SEQ ID NO:67 is a clone designated herein as "DNA46777-1253".

5        Figure 68 shows the amino acid sequence (SEQ ID NO:68) derived from the coding sequence of SEQ ID NO:67 shown in Figure 67.

Figure 69 shows a nucleotide sequence (SEQ ID NO:69) of a native sequence PRO532 cDNA, wherein SEQ ID NO:69 is a clone designated herein as "DNA48335".

10       Figure 70 shows the amino acid sequence (SEQ ID NO:70) derived from the coding sequence of SEQ ID NO:69 shown in Figure 69.

Figure 71 shows a nucleotide sequence (SEQ ID NO:71) of a native sequence PRO322 cDNA, wherein SEQ ID NO:71 is a clone designated herein as "DNA48336-1309".

Figure 72 shows the amino acid sequence (SEQ ID NO:72) derived from the coding sequence of SEQ ID NO:71 shown in Figure 71.

15       Figure 73 shows a nucleotide sequence (SEQ ID NO:73) of a native sequence PRO1120 cDNA, wherein SEQ ID NO:73 is a clone designated herein as "DNA48606-1479".

Figure 74 shows the amino acid sequence (SEQ ID NO:74) derived from the coding sequence of SEQ ID NO:73 shown in Figure 73.

20       Figure 75 shows a nucleotide sequence (SEQ ID NO:75) of a native sequence PRO7261 cDNA, wherein SEQ ID NO:75 is a clone designated herein as "DNA49149".

Figure 76 shows the amino acid sequence (SEQ ID NO:76) derived from the coding sequence of SEQ ID NO:75 shown in Figure 75.

Figure 77 shows a nucleotide sequence (SEQ ID NO:77) of a native sequence PRO533 cDNA, wherein SEQ ID NO:77 is a clone designated herein as "DNA49435-1219".

25       Figure 78 shows the amino acid sequence (SEQ ID NO:78) derived from the coding sequence of SEQ ID NO:77 shown in Figure 77.

Figure 79 shows a nucleotide sequence (SEQ ID NO:79) of a native sequence PRO724 cDNA, wherein SEQ ID NO:79 is a clone designated herein as "DNA49631-1328".

30       Figure 80 shows the amino acid sequence (SEQ ID NO:80) derived from the coding sequence of SEQ ID NO:79 shown in Figure 79.

Figure 81 shows a nucleotide sequence (SEQ ID NO:81) of a native sequence PRO734 cDNA, wherein SEQ ID NO:81 is a clone designated herein as "DNA49817".

Figure 82 shows the amino acid sequence (SEQ ID NO:82) derived from the coding sequence of SEQ ID NO:81 shown in Figure 81.

35       Figure 83 shows a nucleotide sequence (SEQ ID NO:83) of a native sequence PRO771 cDNA, wherein SEQ ID NO:83 is a clone designated herein as "DNA49829-1346".

Figure 84 shows the amino acid sequence (SEQ ID NO:84) derived from the coding sequence of SEQ ID

NO:83 shown in Figure 83.

Figure 85 shows a nucleotide sequence (SEQ ID NO:85) of a native sequence PRO2010 cDNA, wherein SEQ ID NO:85 is a clone designated herein as "DNA50792".

5 Figure 86 shows the amino acid sequence (SEQ ID NO:86) derived from the coding sequence of SEQ ID NO:85 shown in Figure 85.

Figure 87 shows a nucleotide sequence (SEQ ID NO:87) of a native sequence PRO871 cDNA, wherein SEQ ID NO:87 is a clone designated herein as "DNA50919-1361".

Figure 88 shows the amino acid sequence (SEQ ID NO:88) derived from the coding sequence of SEQ ID NO:87 shown in Figure 87.

10 Figure 89 shows a nucleotide sequence (SEQ ID NO:89) of a native sequence PRO697 cDNA, wherein SEQ ID NO:89 is a clone designated herein as "DNA50920-1325".

Figure 90 shows the amino acid sequence (SEQ ID NO:90) derived from the coding sequence of SEQ ID NO:89 shown in Figure 89.

15 Figure 91 shows a nucleotide sequence (SEQ ID NO:91) of a native sequence PRO1083 cDNA, wherein SEQ ID NO:91 is a clone designated herein as "DNA50921-1458".

Figure 92 shows the amino acid sequence (SEQ ID NO:92) derived from the coding sequence of SEQ ID NO:91 shown in Figure 91.

Figure 93 shows a nucleotide sequence (SEQ ID NO:93) of a native sequence PRO725 cDNA, wherein SEQ ID NO:93 is a clone designated herein as "DNA52758-1399".

20 Figure 94 shows the amino acid sequence (SEQ ID NO:94) derived from the coding sequence of SEQ ID NO:93 shown in Figure 93.

Figure 95 shows a nucleotide sequence (SEQ ID NO:95) of a native sequence PRO720 cDNA, wherein SEQ ID NO:95 is a clone designated herein as "DNA53517-1366-1".

25 Figure 96 shows the amino acid sequence (SEQ ID NO:96) derived from the coding sequence of SEQ ID NO:95 shown in Figure 95.

Figure 97 shows a nucleotide sequence (SEQ ID NO:97) of a native sequence PRO738 cDNA, wherein SEQ ID NO:97 is a clone designated herein as "DNA53915-1258".

Figure 98 shows the amino acid sequence (SEQ ID NO:98) derived from the coding sequence of SEQ ID NO:97 shown in Figure 97.

30 Figure 99 shows a nucleotide sequence (SEQ ID NO:99) of a native sequence PRO865 cDNA, wherein SEQ ID NO:99 is a clone designated herein as "DNA53974-1401".

Figure 100 shows the amino acid sequence (SEQ ID NO:100) derived from the coding sequence of SEQ ID NO:99 shown in Figure 99.

35 Figure 101 shows a nucleotide sequence (SEQ ID NO:101) of a native sequence PRO840 cDNA, wherein SEQ ID NO:101 is a clone designated herein as "DNA53987-1438".

Figure 102 shows the amino acid sequence (SEQ ID NO:102) derived from the coding sequence of SEQ ID NO:101 shown in Figure 101.

Figure 103 shows a nucleotide sequence (SEQ ID NO:103) of a native sequence PRO1080 cDNA, wherein SEQ ID NO:103 is a clone designated herein as "DNA56047-1456".

Figure 104 shows the amino acid sequence (SEQ ID NO:104) derived from the coding sequence of SEQ ID NO:103 shown in Figure 103.

5        Figure 105 shows a nucleotide sequence (SEQ ID NO:105) of a native sequence PRO1079 cDNA, wherein SEQ ID NO:105 is a clone designated herein as "DNA56050-1455".

Figure 106 shows the amino acid sequence (SEQ ID NO:106) derived from the coding sequence of SEQ ID NO:105 shown in Figure 105.

10       Figure 107 shows a nucleotide sequence (SEQ ID NO:107) of a native sequence PRO793 cDNA, wherein SEQ ID NO:107 is a clone designated herein as "DNA56110-1437".

Figure 108 shows the amino acid sequence (SEQ ID NO:108) derived from the coding sequence of SEQ ID NO:107 shown in Figure 107.

Figure 109 shows a nucleotide sequence (SEQ ID NO:109) of a native sequence PRO788 cDNA, wherein SEQ ID NO:109 is a clone designated herein as "DNA56405-1357".

15       Figure 110 shows the amino acid sequence (SEQ ID NO:110) derived from the coding sequence of SEQ ID NO:109 shown in Figure 109.

Figure 111 shows a nucleotide sequence (SEQ ID NO:111) of a native sequence PRO938 cDNA, wherein SEQ ID NO:111 is a clone designated herein as "DNA56433-1406".

20       Figure 112 shows the amino acid sequence (SEQ ID NO:112) derived from the coding sequence of SEQ ID NO:111 shown in Figure 111.

Figure 113 shows a nucleotide sequence (SEQ ID NO:113) of a native sequence PRO1012 cDNA, wherein SEQ ID NO:113 is a clone designated herein as "DNA56439-1376".

Figure 114 shows the amino acid sequence (SEQ ID NO:114) derived from the coding sequence of SEQ ID NO:113 shown in Figure 113.

25       Figure 115 shows a nucleotide sequence (SEQ ID NO:115) of a native sequence PRO1477 cDNA, wherein SEQ ID NO:115 is a clone designated herein as "DNA56529-1647".

Figure 116 shows the amino acid sequence (SEQ ID NO:116) derived from the coding sequence of SEQ ID NO:115 shown in Figure 115.

30       Figure 117 shows a nucleotide sequence (SEQ ID NO:117) of a native sequence PRO1134 cDNA, wherein SEQ ID NO:117 is a clone designated herein as "DNA56865-1491".

Figure 118 shows the amino acid sequence (SEQ ID NO:118) derived from the coding sequence of SEQ ID NO:117 shown in Figure 117.

Figure 119 shows a nucleotide sequence (SEQ ID NO:119) of a native sequence PRO162 cDNA, wherein SEQ ID NO:119 is a clone designated herein as "DNA56965-1356".

35       Figure 120 shows the amino acid sequence (SEQ ID NO:120) derived from the coding sequence of SEQ ID NO:119 shown in Figure 119.

Figure 121 shows a nucleotide sequence (SEQ ID NO:121) of a native sequence PRO1114 cDNA, wherein

SEQ ID NO:121 is a clone designated herein as "DNA57033-1403-1".

Figure 122 shows the amino acid sequence (SEQ ID NO:122) derived from the coding sequence of SEQ ID NO:121 shown in Figure 121.

5 Figure 123 shows a nucleotide sequence (SEQ ID NO:123) of a native sequence PRO828 cDNA, wherein SEQ ID NO:123 is a clone designated herein as "DNA57037-1444".

Figure 124 shows the amino acid sequence (SEQ ID NO:124) derived from the coding sequence of SEQ ID NO:123 shown in Figure 123.

Figure 125 shows a nucleotide sequence (SEQ ID NO:125) of a native sequence PRO827 cDNA, wherein SEQ ID NO:125 is a clone designated herein as "DNA57039-1402".

10 Figure 126 shows the amino acid sequence (SEQ ID NO:126) derived from the coding sequence of SEQ ID NO:125 shown in Figure 125.

Figure 127 shows a nucleotide sequence (SEQ ID NO:127) of a native sequence PRO1075 cDNA, wherein SEQ ID NO:127 is a clone designated herein as "DNA57689-1385".

15 Figure 128 shows the amino acid sequence (SEQ ID NO:128) derived from the coding sequence of SEQ ID NO:127 shown in Figure 127.

Figure 129 shows a nucleotide sequence (SEQ ID NO:129) of a native sequence PRO1007 cDNA, wherein SEQ ID NO:129 is a clone designated herein as "DNA57690-1374".

Figure 130 shows the amino acid sequence (SEQ ID NO:130) derived from the coding sequence of SEQ ID NO:129 shown in Figure 129.

20 Figure 131 shows a nucleotide sequence (SEQ ID NO:131) of a native sequence PRO826 cDNA, wherein SEQ ID NO:131 is a clone designated herein as "DNA57694-1341".

Figure 132 shows the amino acid sequence (SEQ ID NO:132) derived from the coding sequence of SEQ ID NO:131 shown in Figure 131.

25 Figure 133 shows a nucleotide sequence (SEQ ID NO:133) of a native sequence PRO819 cDNA, wherein SEQ ID NO:132 is a clone designated herein as "DNA57695-1340".

Figure 134 shows the amino acid sequence (SEQ ID NO:134) derived from the coding sequence of SEQ ID NO:133 shown in Figure 133.

Figure 135 shows a nucleotide sequence (SEQ ID NO:135) of a native sequence PRO1006 cDNA, wherein SEQ ID NO:135 is a clone designated herein as "DNA57699-1412".

30 Figure 136 shows the amino acid sequence (SEQ ID NO:136) derived from the coding sequence of SEQ ID NO:135 shown in Figure 135.

Figure 137 shows a nucleotide sequence (SEQ ID NO:137) of a native sequence PRO982 cDNA, wherein SEQ ID NO:137 is a clone designated herein as "DNA57700-1408".

35 Figure 138 shows the amino acid sequence (SEQ ID NO:138) derived from the coding sequence of SEQ ID NO:137 shown in Figure 137.

Figure 139 shows a nucleotide sequence (SEQ ID NO:139) of a native sequence PRO1005 cDNA, wherein SEQ ID NO:139 is a clone designated herein as "DNA57708-1411".

Figure 140 shows the amino acid sequence (SEQ ID NO:140) derived from the coding sequence of SEQ ID NO:139 shown in Figure 139.

Figure 141 shows a nucleotide sequence (SEQ ID NO:141) of a native sequence PRO791 cDNA, wherein SEQ ID NO:141 is a clone designated herein as "DNA57838-1337".

5       Figure 142 shows the amino acid sequence (SEQ ID NO:142) derived from the coding sequence of SEQ ID NO:141 shown in Figure 141.

Figure 143 shows a nucleotide sequence (SEQ ID NO:143) of a native sequence PRO1071 cDNA, wherein SEQ ID NO:143 is a clone designated herein as "DNA58847-1383".

10       Figure 144 shows the amino acid sequence (SEQ ID NO:144) derived from the coding sequence of SEQ ID NO:143 shown in Figure 43.

Figure 145 shows a nucleotide sequence (SEQ ID NO:145) of a native sequence PRO1415 cDNA, wherein SEQ ID NO:145 is a clone designated herein as "DNA58852-1637".

Figure 146 shows the amino acid sequence (SEQ ID NO:146) derived from the coding sequence of SEQ ID NO:145 shown in Figure 145.

15       Figure 147 shows a nucleotide sequence (SEQ ID NO:147) of a native sequence PRO1054 cDNA, wherein SEQ ID NO:147 is a clone designated herein as "DNA58853-1423".

Figure 148 shows the amino acid sequence (SEQ ID NO:148) derived from the coding sequence of SEQ ID NO:147 shown in Figure 147.

20       Figure 149 shows a nucleotide sequence (SEQ ID NO:149) of a native sequence PRO1411 cDNA, wherein SEQ ID NO:149 is a clone designated herein as "DNA59212-1627".

Figure 150 shows the amino acid sequence (SEQ ID NO:150) derived from the coding sequence of SEQ ID NO:149 shown in Figure 149.

Figure 151 shows a nucleotide sequence (SEQ ID NO:151) of a native sequence PRO1184 cDNA, wherein SEQ ID NO:151 is a clone designated herein as "DNA59220-1514".

25       Figure 152 shows the amino acid sequence (SEQ ID NO:152) derived from the coding sequence of SEQ ID NO:151 shown in Figure 151.

Figure 153 shows a nucleotide sequence (SEQ ID NO:153) of a native sequence PRO1029 cDNA, wherein SEQ ID NO:153 is a clone designated herein as "DNA59493-1420".

30       Figure 154 shows the amino acid sequence (SEQ ID NO:154) derived from the coding sequence of SEQ ID NO:153 shown in Figure 153.

Figure 155 shows a nucleotide sequence (SEQ ID NO:155) of a native sequence PRO1139 cDNA, wherein SEQ ID NO:155 is a clone designated herein as "DNA59497-1496".

Figure 156 shows the amino acid sequence (SEQ ID NO:156) derived from the coding sequence of SEQ ID NO:155 shown in Figure 155.

35       Figure 157 shows a nucleotide sequence (SEQ ID NO:157) of a native sequence PRO1190 cDNA, wherein SEQ ID NO:157 is a clone designated herein as "DNA59586-1520".

Figure 158 shows the amino acid sequence (SEQ ID NO:158) derived from the coding sequence of SEQ

ID NO:157 shown in Figure 157.

Figure 159 shows a nucleotide sequence (SEQ ID NO:159) of a native sequence PRO1309 cDNA, wherein SEQ ID NO:159 is a clone designated herein as "DNA59588-1571".

5 Figure 160 shows the amino acid sequence (SEQ ID NO:160) derived from the coding sequence of SEQ ID NO:159 shown in Figure 159.

Figure 161 shows a nucleotide sequence (SEQ ID NO:161) of a native sequence PRO836 cDNA, wherein SEQ ID NO:161 is a clone designated herein as "DNA59620-1463".

Figure 162 shows the amino acid sequence (SEQ ID NO:162) derived from the coding sequence of SEQ ID NO:161 shown in Figure 161.

10 Figure 163 shows a nucleotide sequence (SEQ ID NO:163) of a native sequence PRO1025 cDNA, wherein SEQ ID NO:163 is a clone designated herein as "DNA59622-1334".

Figure 164 shows the amino acid sequence (SEQ ID NO:164) derived from the coding sequence of SEQ ID NO:163 shown in Figure 163.

15 Figure 165 shows a nucleotide sequence (SEQ ID NO:165) of a native sequence PRO1131 cDNA, wherein SEQ ID NO:165 is a clone designated herein as "DNA59777-1480".

Figure 166 shows the amino acid sequence (SEQ ID NO:166) derived from the coding sequence of SEQ ID NO:165 shown in Figure 165.

Figure 167 shows a nucleotide sequence (SEQ ID NO:167) of a native sequence PRO1182 cDNA, wherein SEQ ID NO:167 is a clone designated herein as "DNA59848-1512".

20 Figure 168 shows the amino acid sequence (SEQ ID NO:168) derived from the coding sequence of SEQ ID NO:167 shown in Figure 167.

Figure 169 shows a nucleotide sequence (SEQ ID NO:169) of a native sequence PRO1155 cDNA, wherein SEQ ID NO:169 is a clone designated herein as "DNA59849-1504".

25 Figure 170 shows the amino acid sequence (SEQ ID NO:170) derived from the coding sequence of SEQ ID NO:169 shown in Figure 169.

Figure 171 shows a nucleotide sequence (SEQ ID NO:171) of a native sequence PRO1186 cDNA, wherein SEQ ID NO:171 is a clone designated herein as "DNA60621-1516".

Figure 172 shows the amino acid sequence (SEQ ID NO:172) derived from the coding sequence of SEQ ID NO:171 shown in Figure 171.

30 Figure 173 shows a nucleotide sequence (SEQ ID NO:173) of a native sequence PRO1198 cDNA, wherein SEQ ID NO:173 is a clone designated herein as "DNA60622-1525".

Figure 174 shows the amino acid sequence (SEQ ID NO:174) derived from the coding sequence of SEQ ID NO:173 shown in Figure 173.

35 Figure 175 shows a nucleotide sequence (SEQ ID NO:175) of a native sequence PRO1265 cDNA, wherein SEQ ID NO:175 is a clone designated herein as "DNA60764-1533".

Figure 176 shows the amino acid sequence (SEQ ID NO:176) derived from the coding sequence of SEQ ID NO:175 shown in Figure 175.



Figure 177 shows a nucleotide sequence (SEQ ID NO:177) of a native sequence PRO1361 cDNA, wherein SEQ ID NO:177 is a clone designated herein as "DNA60783-1611".

Figure 178 shows the amino acid sequence (SEQ ID NO:178) derived from the coding sequence of SEQ ID NO:177 shown in Figure 177.

5        Figure 179 shows a nucleotide sequence (SEQ ID NO:179) of a native sequence PRO1287 cDNA, wherein SEQ ID NO:179 is a clone designated herein as "DNA61755-1554".

Figure 180 shows the amino acid sequence (SEQ ID NO:180) derived from the coding sequence of SEQ ID NO:179 shown in Figure 179.

10       Figure 181 shows a nucleotide sequence (SEQ ID NO:181) of a native sequence PRO1308 cDNA, wherein SEQ ID NO:181 is a clone designated herein as "DNA62306-1570".

Figure 182 shows the amino acid sequence (SEQ ID NO:182) derived from the coding sequence of SEQ ID NO:181 shown in Figure 181.

Figure 183 shows a nucleotide sequence (SEQ ID NO:183) of a native sequence PRO4313 cDNA, wherein SEQ ID NO:183 is a clone designated herein as "DNA62312-2558".

15       Figure 184 shows the amino acid sequence (SEQ ID NO:184) derived from the coding sequence of SEQ ID NO:183 shown in Figure 183.

Figure 185 shows a nucleotide sequence (SEQ ID NO:185) of a native sequence PRO1192 cDNA, wherein SEQ ID NO:185 is a clone designated herein as "DNA62814-1521".

20       Figure 186 shows the amino acid sequence (SEQ ID NO:186) derived from the coding sequence of SEQ ID NO:185 shown in Figure 185.

Figure 187 shows a nucleotide sequence (SEQ ID NO:187) of a native sequence PRO1160 cDNA, wherein SEQ ID NO:187 is a clone designated herein as "DNA62872-1509".

Figure 188 shows the amino acid sequence (SEQ ID NO:188) derived from the coding sequence of SEQ ID NO:187 shown in Figure 187.

25       Figure 189 shows a nucleotide sequence (SEQ ID NO:189) of a native sequence PRO1244 cDNA, wherein SEQ ID NO:189 is a clone designated herein as "DNA64883-1526".

Figure 190 shows the amino acid sequence (SEQ ID NO:190) derived from the coding sequence of SEQ ID NO:189 shown in Figure 189.

30       Figure 191 shows a nucleotide sequence (SEQ ID NO:191) of a native sequence PRO1356 cDNA, wherein SEQ ID NO:191 is a clone designated herein as "DNA64886-1601".

Figure 192 shows the amino acid sequence (SEQ ID NO:192) derived from the coding sequence of SEQ ID NO:191 shown in Figure 191.

Figure 193 shows a nucleotide sequence (SEQ ID NO:193) of a native sequence PRO1274 cDNA, wherein SEQ ID NO:193 is a clone designated herein as "DNA64889-1541".

35       Figure 194 shows the amino acid sequence (SEQ ID NO:194) derived from the coding sequence of SEQ ID NO:193 shown in Figure 193.

Figure 195 shows a nucleotide sequence (SEQ ID NO:195) of a native sequence PRO1272 cDNA, wherein

SEQ ID NO:195 is a clone designated herein as "DNA64896-1539".

Figure 196 shows the amino acid sequence (SEQ ID NO:196) derived from the coding sequence of SEQ ID NO:195 shown in Figure 195.

5 Figure 197 shows a nucleotide sequence (SEQ ID NO:197) of a native sequence PRO1412 cDNA, wherein SEQ ID NO:197 is a clone designated herein as "DNA64897-1628".

Figure 198 shows the amino acid sequence (SEQ ID NO:198) derived from the coding sequence of SEQ ID NO:197 shown in Figure 197.

Figure 199 shows a nucleotide sequence (SEQ ID NO:199) of a native sequence PRO1286 cDNA, wherein SEQ ID NO:199 is a clone designated herein as "DNA64903-1553".

10 Figure 200 shows the amino acid sequence (SEQ ID NO:200) derived from the coding sequence of SEQ ID NO:199 shown in Figure 199.

Figure 201 shows a nucleotide sequence (SEQ ID NO:201) of a native sequence PRO1347 cDNA, wherein SEQ ID NO:201 is a clone designated herein as "DNA64950-1590".

15 Figure 202 shows the amino acid sequence (SEQ ID NO:202) derived from the coding sequence of SEQ ID NO:201 shown in Figure 201.

Figure 203 shows a nucleotide sequence (SEQ ID NO:203) of a native sequence PRO1273 cDNA, wherein SEQ ID NO:203 is a clone designated herein as "DNA65402-1540".

Figure 204 shows the amino acid sequence (SEQ ID NO:204) derived from the coding sequence of SEQ ID NO:203 shown in Figure 203.

20 Figure 205 shows a nucleotide sequence (SEQ ID NO:205) of a native sequence PRO1283 cDNA, wherein SEQ ID NO:205 is a clone designated herein as "DNA65404-1551".

Figure 206 shows the amino acid sequence (SEQ ID NO:206) derived from the coding sequence of SEQ ID NO:205 shown in Figure 205.

25 Figure 207 shows a nucleotide sequence (SEQ ID NO:207) of a native sequence PRO1279 cDNA, wherein SEQ ID NO:207 is a clone designated herein as "DNA65405-1547".

Figure 208 shows the amino acid sequence (SEQ ID NO:208) derived from the coding sequence of SEQ ID NO:207 shown in Figure 207.

Figure 209 shows a nucleotide sequence (SEQ ID NO:209) of a native sequence PRO1306 cDNA, wherein SEQ ID NO:209 is a clone designated herein as "DNA65410-1569".

30 Figure 210 shows the amino acid sequence (SEQ ID NO:210) derived from the coding sequence of SEQ ID NO:209 shown in Figure 209.

Figure 211 shows a nucleotide sequence (SEQ ID NO:211) of a native sequence PRO1195 cDNA, wherein SEQ ID NO:211 is a clone designated herein as "DNA65412-1523".

35 Figure 212 shows the amino acid sequence (SEQ ID NO:212) derived from the coding sequence of SEQ ID NO:211 shown in Figure 211.

Figure 213 shows a nucleotide sequence (SEQ ID NO:213) of a native sequence PRO4995 cDNA, wherein SEQ ID NO:213 is a clone designated herein as "DNA66307-2661".

Figure 214 shows the amino acid sequence (SEQ ID NO:214) derived from the coding sequence of SEQ ID NO:213 shown in Figure 213.

Figure 215 shows a nucleotide sequence (SEQ ID NO:215) of a native sequence PRO1382 cDNA, wherein SEQ ID NO:215 is a clone designated herein as "DNA66526-1616".

5        Figure 216 shows the amino acid sequence (SEQ ID NO:216) derived from the coding sequence of SEQ ID NO:215 shown in Figure 215.

Figure 217 shows a nucleotide sequence (SEQ ID NO:217) of a native sequence PRO1325 cDNA, wherein SEQ ID NO:217 is a clone designated herein as "DNA66659-1593".

10       Figure 218 shows the amino acid sequence (SEQ ID NO:218) derived from the coding sequence of SEQ ID NO:217 shown in Figure 217.

Figure 219 shows a nucleotide sequence (SEQ ID NO:219) of a native sequence PRO1329 cDNA, wherein SEQ ID NO:219 is a clone designated herein as "DNA66660-1585".

Figure 220 shows the amino acid sequence (SEQ ID NO:220) derived from the coding sequence of SEQ ID NO:219 shown in Figure 219.

15       Figure 221 shows a nucleotide sequence (SEQ ID NO:221) of a native sequence PRO1338 cDNA, wherein SEQ ID NO:221 is a clone designated herein as "DNA66667-1596".

Figure 222 shows the amino acid sequence (SEQ ID NO:222) derived from the coding sequence of SEQ ID NO:221 shown in Figure 221.

20       Figure 223 shows a nucleotide sequence (SEQ ID NO:223) of a native sequence PRO1337 cDNA, wherein SEQ ID NO:223 is a clone designated herein as "DNA66672-1586".

Figure 224 shows the amino acid sequence (SEQ ID NO:224) derived from the coding sequence of SEQ ID NO:223 shown in Figure 223.

Figure 225 shows a nucleotide sequence (SEQ ID NO:225) of a native sequence PRO1343 cDNA, wherein SEQ ID NO:225 is a clone designated herein as "DNA66675-1587".

25       Figure 226 shows the amino acid sequence (SEQ ID NO:226) derived from the coding sequence of SEQ ID NO:225 shown in Figure 225.

Figure 227 shows a nucleotide sequence (SEQ ID NO:227) of a native sequence PRO1376 cDNA, wherein SEQ ID NO:227 is a clone designated herein as "DNA67300-1605".

30       Figure 228 shows the amino acid sequence (SEQ ID NO:228) derived from the coding sequence of SEQ ID NO:227 shown in Figure 227.

Figure 229 shows a nucleotide sequence (SEQ ID NO:229) of a native sequence PRO1434 cDNA, wherein SEQ ID NO:229 is a clone designated herein as "DNA68818-2536".

Figure 230 shows the amino acid sequence (SEQ ID NO:230) derived from the coding sequence of SEQ ID NO:229 shown in Figure 229.

35       Figure 231 shows a nucleotide sequence (SEQ ID NO:231) of a native sequence PRO3579 cDNA, wherein SEQ ID NO:231 is a clone designated herein as "DNA68862-2546".

Figure 232 shows the amino acid sequence (SEQ ID NO:232) derived from the coding sequence of SEQ

ID NO:231 shown in Figure 231.

Figure 233 shows a nucleotide sequence (SEQ ID NO:233) of a native sequence PRO1387 cDNA, wherein SEQ ID NO:233 is a clone designated herein as "DNA68872-1620".

5 Figure 234 shows the amino acid sequence (SEQ ID NO:234) derived from the coding sequence of SEQ ID NO:233 shown in Figure 233.

Figure 235 shows a nucleotide sequence (SEQ ID NO:235) of a native sequence PRO1419 cDNA, wherein SEQ ID NO:235 is a clone designated herein as "DNA71290-1630".

Figure 236 shows the amino acid sequence (SEQ ID NO:236) derived from the coding sequence of SEQ ID NO:235 shown in Figure 235.

10 Figure 237 shows a nucleotide sequence (SEQ ID NO:237) of a native sequence PRO1488 cDNA, wherein SEQ ID NO:237 is a clone designated herein as "DNA73736-1657".

Figure 238 shows the amino acid sequence (SEQ ID NO:238) derived from the coding sequence of SEQ ID NO:237 shown in Figure 237.

15 Figure 239 shows a nucleotide sequence (SEQ ID NO:239) of a native sequence PRO1474 cDNA, wherein SEQ ID NO:239 is a clone designated herein as "DNA73739-1645".

Figure 240 shows the amino acid sequence (SEQ ID NO:240) derived from the coding sequence of SEQ ID NO:239 shown in Figure 239.

Figure 241 shows a nucleotide sequence (SEQ ID NO:241) of a native sequence PRO1508 cDNA, wherein SEQ ID NO:241 is a clone designated herein as "DNA73742-1662".

20 Figure 242 shows the amino acid sequence (SEQ ID NO:242) derived from the coding sequence of SEQ ID NO:241 shown in Figure 241.

Figure 243 shows a nucleotide sequence (SEQ ID NO:243) of a native sequence PRO1754 cDNA, wherein SEQ ID NO:243 is a clone designated herein as "DNA76385-1692".

25 Figure 244 shows the amino acid sequence (SEQ ID NO:244) derived from the coding sequence of SEQ ID NO:243 shown in Figure 243.

Figure 245 shows a nucleotide sequence (SEQ ID NO:245) of a native sequence PRO1550 cDNA, wherein SEQ ID NO:245 is a clone designated herein as "DNA76393-1664".

Figure 246 shows the amino acid sequence (SEQ ID NO:246) derived from the coding sequence of SEQ ID NO:245 shown in Figure 245.

30 Figure 247 shows a nucleotide sequence (SEQ ID NO:247) of a native sequence PRO1758 cDNA, wherein SEQ ID NO:247 is a clone designated herein as "DNA76399-1700".

Figure 248 shows the amino acid sequence (SEQ ID NO:248) derived from the coding sequence of SEQ ID NO:247 shown in Figure 247.

35 Figure 249 shows a nucleotide sequence (SEQ ID NO:249) of a native sequence PRO1917 cDNA, wherein SEQ ID NO:249 is a clone designated herein as "DNA76400-2528".

Figure 250 shows the amino acid sequence (SEQ ID NO:250) derived from the coding sequence of SEQ ID NO:249 shown in Figure 249.

Figure 251 shows a nucleotide sequence (SEQ ID NO:251) of a native sequence PRO1787 cDNA, wherein SEQ ID NO:251 is a clone designated herein as "DNA76510-2504".

Figure 252 shows the amino acid sequence (SEQ ID NO:252) derived from the coding sequence of SEQ ID NO:251 shown in Figure 251.

5        Figure 253 shows a nucleotide sequence (SEQ ID NO:253) of a native sequence PRO1556 cDNA, wherein SEQ ID NO:253 is a clone designated herein as "DNA76529-1666".

Figure 254 shows the amino acid sequence (SEQ ID NO:254) derived from the coding sequence of SEQ ID NO:253 shown in Figure 253.

10       Figure 255 shows a nucleotide sequence (SEQ ID NO:255) of a native sequence PRO1760 cDNA, wherein SEQ ID NO:255 is a clone designated herein as "DNA76532-1702".

Figure 256 shows the amino acid sequence (SEQ ID NO:256) derived from the coding sequence of SEQ ID NO:255 shown in Figure 255.

Figure 257 shows a nucleotide sequence (SEQ ID NO:257) of a native sequence PRO1567 cDNA, wherein SEQ ID NO:257 is a clone designated herein as "DNA76541-1675".

15       Figure 258 shows the amino acid sequence (SEQ ID NO:258) derived from the coding sequence of SEQ ID NO:257 shown in Figure 257.

Figure 259 shows a nucleotide sequence (SEQ ID NO:259) of a native sequence PRO1600 cDNA, wherein SEQ ID NO:259 is a clone designated herein as "DNA77503-1686".

20       Figure 260 shows the amino acid sequence (SEQ ID NO:260) derived from the coding sequence of SEQ ID NO:259 shown in Figure 259.

Figure 261 shows a nucleotide sequence (SEQ ID NO:261) of a native sequence PRO1868 cDNA, wherein SEQ ID NO:261 is a clone designated herein as "DNA77624-2515".

Figure 262 shows the amino acid sequence (SEQ ID NO:262) derived from the coding sequence of SEQ ID NO:261 shown in Figure 261.

25       Figure 263 shows a nucleotide sequence (SEQ ID NO:263) of a native sequence PRO1890 cDNA, wherein SEQ ID NO:263 is a clone designated herein as "DNA79230-2525".

Figure 264 shows the amino acid sequence (SEQ ID NO:264) derived from the coding sequence of SEQ ID NO:263 shown in Figure 263.

30       Figure 265 shows a nucleotide sequence (SEQ ID NO:265) of a native sequence PRO1887 cDNA, wherein SEQ ID NO:265 is a clone designated herein as "DNA79862-2522".

Figure 266 shows the amino acid sequence (SEQ ID NO:265) derived from the coding sequence of SEQ ID NO:265 shown in Figure 265.

Figure 267 shows a nucleotide sequence (SEQ ID NO:267) of a native sequence PRO4353 cDNA, wherein SEQ ID NO:267 is a clone designated herein as "DNA80145-2594".

35       Figure 268 shows the amino acid sequence (SEQ ID NO:268) derived from the coding sequence of SEQ ID NO:267 shown in Figure 267.

Figure 269 shows a nucleotide sequence (SEQ ID NO:269) of a native sequence PRO1782 cDNA, wherein

SEQ ID NO:269 is a clone designated herein as "DNA80899-2501".

Figure 270 shows the amino acid sequence (SEQ ID NO:270) derived from the coding sequence of SEQ ID NO:269 shown in Figure 269.

5 Figure 271 shows a nucleotide sequence (SEQ ID NO:271) of a native sequence PRO1928 cDNA, wherein SEQ ID NO:271 is a clone designated herein as "DNA81754-2532".

Figure 272 shows the amino acid sequence (SEQ ID NO:272) derived from the coding sequence of SEQ ID NO:271 shown in Figure 271.

Figure 273 shows a nucleotide sequence (SEQ ID NO:273) of a native sequence PRO1865 cDNA, wherein SEQ ID NO:273 is a clone designated herein as "DNA81757-2512".

10 Figure 274 shows the amino acid sequence (SEQ ID NO:274) derived from the coding sequence of SEQ ID NO:273 shown in Figure 273.

Figure 275 shows a nucleotide sequence (SEQ ID NO:275) of a native sequence PRO4341 cDNA, wherein SEQ ID NO:275 is a clone designated herein as "DNA81761-2583".

15 Figure 276 shows the amino acid sequence (SEQ ID NO:276) derived from the coding sequence of SEQ ID NO:275 shown in Figure 275.

Figure 277 shows a nucleotide sequence (SEQ ID NO:277) of a native sequence PRO6714 cDNA, wherein SEQ ID NO:277 is a clone designated herein as "DNA82358-2738".

Figure 278 shows the amino acid sequence (SEQ ID NO:278) derived from the coding sequence of SEQ ID NO:277 shown in Figure 277.

20 Figure 279 shows a nucleotide sequence (SEQ ID NO:279) of a native sequence PRO5723 cDNA, wherein SEQ ID NO:279 is a clone designated herein as "DNA82361".

Figure 280 shows the amino acid sequence (SEQ ID NO:280) derived from the coding sequence of SEQ ID NO:279 shown in Figure 279.

25 Figure 281 shows a nucleotide sequence (SEQ ID NO:281) of a native sequence PRO3438 cDNA, wherein SEQ ID NO:281 is a clone designated herein as "DNA82364-2538".

Figure 282 shows the amino acid sequence (SEQ ID NO:282) derived from the coding sequence of SEQ ID NO:281 shown in Figure 281.

Figure 283 shows a nucleotide sequence (SEQ ID NO:283) of a native sequence PRO6071 cDNA, wherein SEQ ID NO:283 is a clone designated herein as "DNA82403-2959".

30 Figure 284 shows the amino acid sequence (SEQ ID NO:284) derived from the coding sequence of SEQ ID NO:283 shown in Figure 283.

Figure 285 shows a nucleotide sequence (SEQ ID NO:285) of a native sequence PRO1801 cDNA, wherein SEQ ID NO:285 is a clone designated herein as "DNA83500-2506".

35 Figure 286 shows the amino acid sequence (SEQ ID NO:286) derived from the coding sequence of SEQ ID NO:285 shown in Figure 285.

Figure 287 shows a nucleotide sequence (SEQ ID NO:287) of a native sequence PRO4324 cDNA, wherein SEQ ID NO:287 is a clone designated herein as "DNA83560-2569".

Figure 288 shows the amino acid sequence (SEQ ID NO:288) derived from the coding sequence of SEQ ID NO:287 shown in Figure 287.

Figure 289 shows a nucleotide sequence (SEQ ID NO:289) of a native sequence PRO4333 cDNA, wherein SEQ ID NO:289 is a clone designated herein as "DNA84210-2576".

5        Figure 290 shows the amino acid sequence (SEQ ID NO:290) derived from the coding sequence of SEQ ID NO:289 shown in Figure 289.

Figure 291 shows a nucleotide sequence (SEQ ID NO:291) of a native sequence PRO4405 cDNA, wherein SEQ ID NO:291 is a clone designated herein as "DNA84920-2614".

10       Figure 292 shows the amino acid sequence (SEQ ID NO:292) derived from the coding sequence of SEQ ID NO:291 shown in Figure 291.

Figure 293 shows a nucleotide sequence (SEQ ID NO:293) of a native sequence PRO4356 cDNA, wherein SEQ ID NO:293 is a clone designated herein as "DNA86576-2595".

Figure 294 shows the amino acid sequence (SEQ ID NO:294) derived from the coding sequence of SEQ ID NO:293 shown in Figure 293.

15       Figure 295 shows a nucleotide sequence (SEQ ID NO:295) of a native sequence PRO3444 cDNA, wherein SEQ ID NO:295 is a clone designated herein as "DNA87997".

Figure 296 shows the amino acid sequence (SEQ ID NO:296) derived from the coding sequence of SEQ ID NO:295 shown in Figure 295.

20       Figure 297 shows a nucleotide sequence (SEQ ID NO:297) of a native sequence PRO4302 cDNA, wherein SEQ ID NO:297 is a clone designated herein as "DNA92218-2554".

Figure 298 shows the amino acid sequence (SEQ ID NO:298) derived from the coding sequence of SEQ ID NO:297 shown in Figure 297.

Figure 299 shows a nucleotide sequence (SEQ ID NO:299) of a native sequence PRO4371 cDNA, wherein SEQ ID NO:299 is a clone designated herein as "DNA92233-2599".

25       Figure 300 shows the amino acid sequence (SEQ ID NO:300) derived from the coding sequence of SEQ ID NO:299 shown in Figure 299.

Figure 301 shows a nucleotide sequence (SEQ ID NO:301) of a native sequence PRO4354 cDNA, wherein SEQ ID NO:301 is a clone designated herein as "DNA92256-2596".

30       Figure 302 shows the amino acid sequence (SEQ ID NO:302) derived from the coding sequence of SEQ ID NO:301 shown in Figure 301.

Figure 303 shows a nucleotide sequence (SEQ ID NO:303) of a native sequence PRO5725 cDNA, wherein SEQ ID NO:303 is a clone designated herein as "DNA92265-2669".

Figure 304 shows the amino acid sequence (SEQ ID NO:304) derived from the coding sequence of SEQ ID NO:303 shown in Figure 303.

35       Figure 305 shows a nucleotide sequence (SEQ ID NO:305) of a native sequence PRO4408 cDNA, wherein SEQ ID NO:305 is a clone designated herein as "DNA92274-2617".

Figure 306 shows the amino acid sequence (SEQ ID NO:306) derived from the coding sequence of SEQ

ID NO:305 shown in Figure 305.

Figure 307 shows a nucleotide sequence (SEQ ID NO:307) of a native sequence PRO9940 cDNA, wherein SEQ ID NO:307 is a clone designated herein as "DNA92282".

5 Figure 308 shows the amino acid sequence (SEQ ID NO:308) derived from the coding sequence of SEQ ID NO:307 shown in Figure 307.

Figure 309 shows a nucleotide sequence (SEQ ID NO:309) of a native sequence PRO5737 cDNA, wherein SEQ ID NO:309 is a clone designated herein as "DNA92929-2534-1".

Figure 310 shows the amino acid sequence (SEQ ID NO:310) derived from the coding sequence of SEQ ID NO:309 shown in Figure 309.

10 Figure 311 shows a nucleotide sequence (SEQ ID NO:311) of a native sequence PRO4425 cDNA, wherein SEQ ID NO:311 is a clone designated herein as "DNA93011-2637".

Figure 312 shows the amino acid sequence (SEQ ID NO:312) derived from the coding sequence of SEQ ID NO:311 shown in Figure 311.

15 Figure 313 shows a nucleotide sequence (SEQ ID NO:313) of a native sequence PRO4345 cDNA, wherein SEQ ID NO:313 is a clone designated herein as "DNA94854-2586".

Figure 314 shows the amino acid sequence (SEQ ID NO:314) derived from the coding sequence of SEQ ID NO:313 shown in Figure 313.

Figure 315 shows a nucleotide sequence (SEQ ID NO:315) of a native sequence PRO4342 cDNA, wherein SEQ ID NO:315 is a clone designated herein as "DNA96787-2534-1".

20 Figure 316 shows the amino acid sequence (SEQ ID NO:316) derived from the coding sequence of SEQ ID NO:315 shown in Figure 315.

Figure 317 shows a nucleotide sequence (SEQ ID NO:317) of a native sequence PRO3562 cDNA, wherein SEQ ID NO:317 is a clone designated herein as "DNA96791".

25 Figure 318 shows the amino acid sequence (SEQ ID NO:318) derived from the coding sequence of SEQ ID NO:317 shown in Figure 317.

Figure 319 shows a nucleotide sequence (SEQ ID NO:319) of a native sequence PRO4422 cDNA, wherein SEQ ID NO:319 is a clone designated herein as "DNA96867-2620".

Figure 320 shows the amino acid sequence (SEQ ID NO:320) derived from the coding sequence of SEQ ID NO:319 shown in Figure 319.

30 Figure 321 shows a nucleotide sequence (SEQ ID NO:321) of a native sequence PRO5776 cDNA, wherein SEQ ID NO:321 is a clone designated herein as "DNA96872-2674".

Figure 322 shows the amino acid sequence (SEQ ID NO:322) derived from the coding sequence of SEQ ID NO:321 shown in Figure 321.

35 Figure 323 shows a nucleotide sequence (SEQ ID NO:323) of a native sequence PRO4430 cDNA, wherein SEQ ID NO:323 is a clone designated herein as "DNA96878-2626".

Figure 324 shows the amino acid sequence (SEQ ID NO:324) derived from the coding sequence of SEQ ID NO:323 shown in Figure 323.



Figure 325 shows a nucleotide sequence (SEQ ID NO:325) of a native sequence PRO4499 cDNA, wherein SEQ ID NO:325 is a clone designated herein as "DNA96889-2641".

Figure 326 shows the amino acid sequence (SEQ ID NO:326) derived from the coding sequence of SEQ ID NO:325 shown in Figure 325.

5        Figure 327 shows a nucleotide sequence (SEQ ID NO:327) of a native sequence PRO4503 cDNA, wherein SEQ ID NO:327 is a clone designated herein as "DNA100312-2645".

Figure 328 shows the amino acid sequence (SEQ ID NO:328) derived from the coding sequence of SEQ ID NO:327 shown in Figure 327.

10       Figure 329 shows a nucleotide sequence (SEQ ID NO:329) of a native sequence PRO10008 cDNA, wherein SEQ ID NO:329 is a clone designated herein as "DNA101921".

Figure 330 shows the amino acid sequence (SEQ ID NO:330) derived from the coding sequence of SEQ ID NO:329 shown in Figure 329.

Figure 331 shows a nucleotide sequence (SEQ ID NO:331) of a native sequence PRO5730 cDNA, wherein SEQ ID NO:331 is a clone designated herein as "DNA101926".

15       Figure 332 shows the amino acid sequence (SEQ ID NO:332) derived from the coding sequence of SEQ ID NO:331 shown in Figure 331.

Figure 333 shows a nucleotide sequence (SEQ ID NO:333) of a native sequence PRO6008 cDNA, wherein SEQ ID NO:333 is a clone designated herein as "DNA102844".

20       Figure 334 shows the amino acid sequence (SEQ ID NO:334) derived from the coding sequence of SEQ ID NO:333 shown in Figure 333.

Figure 335 shows a nucleotide sequence (SEQ ID NO:335) of a native sequence PRO4527 cDNA, wherein SEQ ID NO:335 is a clone designated herein as "DNA103197".

Figure 336 shows the amino acid sequence (SEQ ID NO:336) derived from the coding sequence of SEQ ID NO:335 shown in Figure 335.

25       Figure 337 shows a nucleotide sequence (SEQ ID NO:337) of a native sequence PRO4538 cDNA, wherein SEQ ID NO:337 is a clone designated herein as "DNA103208".

Figure 338 shows the amino acid sequence (SEQ ID NO:338) derived from the coding sequence of SEQ ID NO:337 shown in Figure 337.

30       Figure 339 shows a nucleotide sequence (SEQ ID NO:339) of a native sequence PRO4553 cDNA, wherein SEQ ID NO:339 is a clone designated herein as "DNA103223".

Figure 340 shows the amino acid sequence (SEQ ID NO:340) derived from the coding sequence of SEQ ID NO:339 shown in Figure 339.

Figure 341 shows a nucleotide sequence (SEQ ID NO:341) of a native sequence PRO6006 cDNA, wherein SEQ ID NO:341 is a clone designated herein as "DNA105782-2693".

35       Figure 342 shows the amino acid sequence (SEQ ID NO:342) derived from the coding sequence of SEQ ID NO:341 shown in Figure 341.

Figure 343 shows a nucleotide sequence (SEQ ID NO:343) of a native sequence PRO6029 cDNA, wherein

SEQ ID NO:343 is a clone designated herein as "DNA105849-2704".

Figure 344 shows the amino acid sequence (SEQ ID NO:344) derived from the coding sequence of SEQ ID NO:343 shown in Figure 343.

5 Figure 345 shows a nucleotide sequence (SEQ ID NO:345) of a native sequence PRO9821 cDNA, wherein SEQ ID NO:345 is a clone designated herein as "DNA108725-2766".

Figure 346 shows the amino acid sequence (SEQ ID NO:346) derived from the coding sequence of SEQ ID NO:345 shown in Figure 345.

Figure 347 shows a nucleotide sequence (SEQ ID NO:347) of a native sequence PRO9820 cDNA, wherein SEQ ID NO:347 is a clone designated herein as "DNA108769-2765".

10 Figure 348 shows the amino acid sequence (SEQ ID NO:348) derived from the coding sequence of SEQ ID NO:347 shown in Figure 347.

Figure 349 shows a nucleotide sequence (SEQ ID NO:349) of a native sequence PRO9771 cDNA, wherein SEQ ID NO:349 is a clone designated herein as "DNA119498-2965".

15 Figure 350 shows the amino acid sequence (SEQ ID NO:350) derived from the coding sequence of SEQ ID NO:349 shown in Figure 349.

Figure 351 shows a nucleotide sequence (SEQ ID NO:351) of a native sequence PRO7436 cDNA, wherein SEQ ID NO:351 is a clone designated herein as "DNA119535-2756".

Figure 352 shows the amino acid sequence (SEQ ID NO:352) derived from the coding sequence of SEQ ID NO:351 shown in Figure 351.

20 Figure 353 shows a nucleotide sequence (SEQ ID NO:353) of a native sequence PRO10096 cDNA, wherein SEQ ID NO:353 is a clone designated herein as "DNA125185-2806".

Figure 354 shows the amino acid sequence (SEQ ID NO:354) derived from the coding sequence of SEQ ID NO:353 shown in Figure 353.

25 Figure 355 shows a nucleotide sequence (SEQ ID NO:355) of a native sequence PRO19670 cDNA, wherein SEQ ID NO:355 is a clone designated herein as "DNA131639-2874".

Figure 356 shows the amino acid sequence (SEQ ID NO:356) derived from the coding sequence of SEQ ID NO:355 shown in Figure 355.

Figure 357 shows a nucleotide sequence (SEQ ID NO:357) of a native sequence PRO20044 cDNA, wherein SEQ ID NO:357 is a clone designated herein as "DNA139623-2893".

30 Figure 358 shows the amino acid sequence (SEQ ID NO:358) derived from the coding sequence of SEQ ID NO:357 shown in Figure 357.

Figure 359 shows a nucleotide sequence (SEQ ID NO:359) of a native sequence PRO9873 cDNA, wherein SEQ ID NO:359 is a clone designated herein as "DNA143076-2787".

35 Figure 360 shows the amino acid sequence (SEQ ID NO:360) derived from the coding sequence of SEQ ID NO:359 shown in Figure 359.

Figure 361 shows a nucleotide sequence (SEQ ID NO:361) of a native sequence PRO21366 cDNA, wherein SEQ ID NO:361 is a clone designated herein as "DNA143276-2975".

Figure 362 shows the amino acid sequence (SEQ ID NO:362) derived from the coding sequence of SEQ ID NO:361 shown in Figure 361.

Figure 363 shows a nucleotide sequence (SEQ ID NO:363) of a native sequence PRO20040 cDNA, wherein SEQ ID NO:363 is a clone designated herein as "DNA164625-2890".

5 Figure 364 shows the amino acid sequence (SEQ ID NO:364) derived from the coding sequence of SEQ ID NO:363 shown in Figure 363.

Figure 365 shows a nucleotide sequence (SEQ ID NO:365) of a native sequence PRO21184 cDNA, wherein SEQ ID NO:365 is a clone designated herein as "DNA167678-2963".

10 Figure 366 shows the amino acid sequence (SEQ ID NO:366) derived from the coding sequence of SEQ ID NO:365 shown in Figure 365.

Figure 367 shows a nucleotide sequence (SEQ ID NO:367) of a native sequence PRO21055 cDNA, wherein SEQ ID NO:367 is a clone designated herein as "DNA170021-2923".

Figure 368 shows the amino acid sequence (SEQ ID NO:368) derived from the coding sequence of SEQ ID NO:367 shown in Figure 367.

15 Figure 369 shows a nucleotide sequence (SEQ ID NO:369) of a native sequence PRO28631 cDNA, wherein SEQ ID NO:369 is a clone designated herein as "DNA170212-3000".

Figure 370 shows the amino acid sequence (SEQ ID NO:370) derived from the coding sequence of SEQ ID NO:369 shown in Figure 369.

20 Figure 371 shows a nucleotide sequence (SEQ ID NO:371) of a native sequence PRO21384 cDNA, wherein SEQ ID NO:371 is a clone designated herein as "DNA177313-2982".

Figure 372 shows the amino acid sequence (SEQ ID NO:372) derived from the coding sequence of SEQ ID NO:371 shown in Figure 371.

Figure 373 shows a nucleotide sequence (SEQ ID NO:373) of a native sequence PRO1449 cDNA, wherein SEQ ID NO:373 is a clone designated herein as "DNA64908-1163-1".

25 Figure 374 shows the amino acid sequence (SEQ ID NO:374) derived from the coding sequence of SEQ ID NO:373 shown in Figure 373.

30 Figure 375 shows wholemount in situ hybridization results on mouse embryos using a mouse orthologue of PRO1449 which has about 78% amino acid identity with PRO1449. The results show that PRO1449 orthologue is expressed in the developing vasculature. The cross-section further shows expression in endothelial cells and progenitors of endothelial cells.

Figure 376 shows that a PRO1449 orthologue having about 78% amino acid identity with PRO1449 is expressed in vasculature of many inflamed and diseased tissues, but is very low, or lacking, in normal adult vessels.

Figure 377 shows that a PRO1449 orthologue having about 78% amino acid identity with PRO1449 induces ectopic vessels in the eyes of chicken embryos.

35

## 5. Detailed Description of the Invention

### 5.1. Definitions

The phrases "cardiovascular, endothelial and angiogenic disorder", "cardiovascular, endothelial and angiogenic dysfunction", "cardiovascular, endothelial or angiogenic disorder" and "cardiovascular, endothelial or angiogenic dysfunction" are used interchangeably and refer in part to systemic disorders that affect vessels, such as diabetes mellitus, as well as diseases of the vessels themselves, such as of the arteries, capillaries, veins, and/or lymphatics. This would include indications that stimulate angiogenesis and/or cardiovascularization, and those that inhibit angiogenesis and/or cardiovascularization. Such disorders include, for example, arterial disease, such as atherosclerosis, hypertension, inflammatory vasculitides, Reynaud's disease and Reynaud's phenomenon, aneurysms, and arterial restenosis; venous and lymphatic disorders such as thrombophlebitis, lymphangitis, and lymphedema; and other vascular disorders such as peripheral vascular disease, cancer such as vascular tumors, *e.g.*, hemangioma (capillary and cavernous), glomus tumors, telangiectasia, bacillary angiomatosis, hemangioendothelioma, angiosarcoma, haemangiopericytoma, Kaposi's sarcoma, lymphangioma, and lymphangiosarcoma, tumor angiogenesis, trauma such as wounds, burns, and other injured tissue, implant fixation, scarring, ischemia reperfusion injury, rheumatoid arthritis, cerebrovascular disease, renal diseases such as acute renal failure, and osteoporosis. This would also include angina, myocardial infarctions such as acute myocardial infarctions, cardiac hypertrophy, and heart failure such as CHF.

"Hypertrophy", as used herein, is defined as an increase in mass of an organ or structure independent of natural growth that does not involve tumor formation. Hypertrophy of an organ or tissue is due either to an increase in the mass of the individual cells (true hypertrophy), or to an increase in the number of cells making up the tissue (hyperplasia), or both. Certain organs, such as the heart, lose the ability to divide shortly after birth. Accordingly, "cardiac hypertrophy" is defined as an increase in mass of the heart, which, in adults, is characterized by an increase in myocyte cell size and contractile protein content without concomitant cell division. The character of the stress responsible for inciting the hypertrophy, (*e.g.*, increased preload, increased afterload, loss of myocytes, as in myocardial infarction, or primary depression of contractility), appears to play a critical role in determining the nature of the response. The early stage of cardiac hypertrophy is usually characterized morphologically by increases in the size of myofibrils and mitochondria, as well as by enlargement of mitochondria and nuclei. At this stage, while muscle cells are larger than normal, cellular organization is largely preserved. At a more advanced stage of cardiac hypertrophy, there are preferential increases in the size or number of specific organelles, such as mitochondria, and new contractile elements are added in localized areas of the cells, in an irregular manner. Cells subjected to long-standing hypertrophy show more obvious disruptions in cellular organization, including markedly enlarged nuclei with highly lobulated membranes, which displace adjacent myofibrils and cause breakdown of normal Z-band registration. The phrase "cardiac hypertrophy" is used to include all stages of the progression of this condition, characterized by various degrees of structural damage of the heart muscle, regardless of the underlying cardiac disorder. Hence, the term also includes physiological conditions instrumental in the development of cardiac hypertrophy, such as elevated blood pressure, aortic stenosis, or myocardial infarction.

"Heart failure" refers to an abnormality of cardiac function where the heart does not pump blood at the rate

needed for the requirements of metabolizing tissues. The heart failure can be caused by a number of factors, including ischemic, congenital, rheumatic, or idiopathic forms.

“Congestive heart failure” (CHF) is a progressive pathologic state where the heart is increasingly unable to supply adequate cardiac output (the volume of blood pumped by the heart over time) to deliver the oxygenated blood to peripheral tissues. As CHF progresses, structural and hemodynamic damages occur. While these damages have a variety of manifestations, one characteristic symptom is ventricular hypertrophy. CHF is a common end result of a number of various cardiac disorders.

“Myocardial infarction” generally results from atherosclerosis of the coronary arteries, often with superimposed coronary thrombosis. It may be divided into two major types: transmural infarcts, in which myocardial necrosis involves the full thickness of the ventricular wall, and subendocardial (nontransmural) infarcts, in which the necrosis involves the subendocardium, the intramural myocardium, or both, without extending all the way through the ventricular wall to the epicardium. Myocardial infarction is known to cause both a change in hemodynamic effects and an alteration in structure in the damaged and healthy zones of the heart. Thus, for example, myocardial infarction reduces the maximum cardiac output and the stroke volume of the heart. Also associated with myocardial infarction is a stimulation of the DNA synthesis occurring in the interstice as well as an increase in the formation of collagen in the areas of the heart not affected.

As a result of the increased stress or strain placed on the heart in prolonged hypertension due, for example, to the increased total peripheral resistance, cardiac hypertrophy has long been associated with “hypertension”. A characteristic of the ventricle that becomes hypertrophic as a result of chronic pressure overload is an impaired diastolic performance. Fouad *et al.*, J. Am. Coll. Cardiol., 4: 1500-1506 (1984); Smith *et al.*, J. Am. Coll. Cardiol., 5: 869-874 (1985). A prolonged left ventricular relaxation has been detected in early essential hypertension, in spite of normal or supranormal systolic function. Hartford *et al.*, Hypertension, 6: 329-338 (1984). However, there is no close parallelism between blood pressure levels and cardiac hypertrophy. Although improvement in left ventricular function in response to antihypertensive therapy has been reported in humans, patients variously treated with a diuretic (hydrochlorothiazide), a  $\beta$ -blocker (propranolol), or a calcium channel blocker (diltiazem), have shown reversal of left ventricular hypertrophy, without improvement in diastolic function. Inouye *et al.*, Am. J. Cardiol., 53: 1583-7 (1984).

Another complex cardiac disease associated with cardiac hypertrophy is “hypertrophic cardiomyopathy”. This condition is characterized by a great diversity of morphologic, functional, and clinical features (Maron *et al.*, N. Engl. J. Med., 316: 780-789 (1987); Spirito *et al.*, N. Engl. J. Med., 320: 749-755 (1989); Louie and Edwards, Prog. Cardiovasc. Dis., 36: 275-308 (1994); Wigle *et al.*, Circulation, 92: 1680-1692 (1995)), the heterogeneity of which is accentuated by the fact that it afflicts patients of all ages. Spirito *et al.*, N. Engl. J. Med., 336: 775-785 (1997). The causative factors of hypertrophic cardiomyopathy are also diverse and little understood. In general, mutations in genes encoding sarcomeric proteins are associated with hypertrophic cardiomyopathy. Recent data suggest that  $\beta$ -myosin heavy chain mutations may account for approximately 30 to 40 percent of cases of familial hypertrophic cardiomyopathy. Watkins *et al.*, N. Engl. J. Med., 326: 1108-1114 (1992); Schwartz *et al.*, Circulation, 91: 532-540 (1995); Marian and Roberts, Circulation, 92: 1336-1347 (1995); Thierfelder *et al.*, Cell, 77: 701-712

(1994); Watkins *et al.*, Nat. Gen., 11: 434-437 (1995). Besides  $\beta$ -myosin heavy chain, other locations of genetic mutations include cardiac troponin T, alpha topomyosin, cardiac myosin binding protein C, essential myosin light chain, and regulatory myosin light chain. See, Malik and Watkins, Curr. Opin. Cardiol., 12: 295-302 (1997).

Supravalvular "aortic stenosis" is an inherited vascular disorder characterized by narrowing of the ascending aorta, but other arteries, including the pulmonary arteries, may also be affected. Untreated aortic stenosis may lead to increased intracardiac pressure resulting in myocardial hypertrophy and eventually heart failure and death. The pathogenesis of this disorder is not fully understood, but hypertrophy and possibly hyperplasia of medial smooth muscle are prominent features of this disorder. It has been reported that molecular variants of the elastin gene are involved in the development and pathogenesis of aortic stenosis. U.S. Patent No. 5,650,282 issued July 22, 1997.

"Valvular regurgitation" occurs as a result of heart diseases resulting in disorders of the cardiac valves. Various diseases, like rheumatic fever, can cause the shrinking or pulling apart of the valve orifice, while other diseases may result in endocarditis, an inflammation of the endocardium or lining membrane of the atrioventricular orifices and operation of the heart. Defects such as the narrowing of the valve stenosis or the defective closing of the valve result in an accumulation of blood in the heart cavity or regurgitation of blood past the valve. If uncorrected, prolonged valvular stenosis or insufficiency may result in cardiac hypertrophy and associated damage to the heart muscle, which may eventually necessitate valve replacement.

The treatment of all these, and other cardiovascular, endothelial and angiogenic disorders, which may or may not be accompanied by cardiac hypertrophy, is encompassed by the present invention.

The terms "cancer", "cancerous", and "malignant" refer to or describe the physiological condition in mammals that is typically characterized by unregulated cell growth. Examples of cancer include but are not limited to, carcinoma including adenocarcinoma, lymphoma, blastoma, melanoma, sarcoma, and leukemia. More particular examples of such cancers include squamous cell cancer, small-cell lung cancer, non-small cell lung cancer, gastrointestinal cancer, Hodgkin's and non-Hodgkin's lymphoma, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer such as hepatic carcinoma and hepatoma, bladder cancer, breast cancer, colon cancer, colorectal cancer, endometrial carcinoma, salivary gland carcinoma, kidney cancer such as renal cell carcinoma and Wilms' tumors, basal cell carcinoma, melanoma, prostate cancer, vulval cancer, thyroid cancer, testicular cancer, esophageal cancer, and various types of head and neck cancer. The preferred cancers for treatment herein are breast, colon, lung, melanoma, ovarian, and others involving vascular tumors as noted above.

The term "cytotoxic agent" as used herein refers to a substance that inhibits or prevents the function of cells and/or causes destruction of cells. The term is intended to include radioactive isotopes (e.g.,  $^{131}\text{I}$ ,  $^{125}\text{I}$ ,  $^{90}\text{Y}$ , and  $^{186}\text{Re}$ ), chemotherapeutic agents, and toxins such as enzymatically active toxins of bacterial, fungal, plant, or animal origin, or fragments thereof.

A "chemotherapeutic agent" is a chemical compound useful in the treatment of cancer. Examples of chemotherapeutic agents include alkylating agents, folic acid antagonists, anti-metabolites of nucleic acid metabolism, antibiotics, pyrimidine analogs, 5-fluorouracil, cisplatin, purine nucleosides, amines, amino acids, triazol nucleosides, or corticosteroids. Specific examples include Adriamycin, Doxorubicin, 5-Fluorouracil,

Cytosine arabinoside ("Ara-C"), Cyclophosphamide, Thiotepa, Busulfan, Cytosin, Taxol, Toxotere, Methotrexate, Cisplatin, Melphalan, Vinblastine, Bleomycin, Etoposide, Ifosfamide, Mitomycin C, Mitoxantrone, Vincristine, Vinorelbine, Carboplatin, Teniposide, Daunomycin, Carminomycin, Aminopterin, Dactinomycin, Mitomycins, Esperamicins (see U.S. Pat. No. 4,675,187), Melphalan, and other related nitrogen mustards. Also included in this definition are hormonal agents that act to regulate or inhibit hormone action on tumors, such as tamoxifen and onapristone.

A "growth-inhibitory agent" when used herein refers to a compound or composition that inhibits growth of a cell, such as an Wnt-overexpressing cancer cell, either *in vitro* or *in vivo*. Thus, the growth-inhibitory agent is one which significantly reduces the percentage of malignant cells in S phase. Examples of growth-inhibitory agents include agents that block cell cycle progression (at a place other than S phase), such as agents that induce G1 arrest and M-phase arrest. Classical M-phase blockers include the vincas (vincristine and vinblastine), taxol, and topo II inhibitors such as doxorubicin, daunorubicin, etoposide, and bleomycin. Those agents that arrest G1 also spill over into S-phase arrest, for example, DNA alkylating agents such as tamoxifen, prednisone, dacarbazine, mechlorethamine, cisplatin, methotrexate, 5-fluorouracil, and ara-C. Further information can be found in The Molecular Basis of Cancer, Mendelsohn and Israel, eds., Chapter 1, entitled "Cell cycle regulation, oncogenes, and antineoplastic drugs" by Murakami *et al.* (WB Saunders: Philadelphia, 1995), especially p. 13. Additional examples include tumor necrosis factor (TNF), an antibody capable of inhibiting or neutralizing the angiogenic activity of acidic or basic FGF or hepatocyte growth factor (HGF), an antibody capable of inhibiting or neutralizing the coagulant activities of tissue factor, protein C, or protein S (see, WO 91/01753, published 21 February 1991), or an antibody capable of binding to HER2 receptor (WO 89/06692), such as the 4D5 antibody (and functional equivalents thereof) (e.g., WO 92/22653).

"Treatment" is an intervention performed with the intention of preventing the development or altering the pathology of a cardiovascular, endothelial, and angiogenic disorder. The concept of treatment is used in the broadest sense, and specifically includes the prevention (prophylaxis), moderation, reduction, and curing of cardiovascular, endothelial, and angiogenic disorders of any stage. Accordingly, "treatment" refers to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) or ameliorate a cardiovascular, endothelial, and angiogenic disorder such as hypertrophy. Those in need of treatment include those already with the disorder as well as those prone to have the disorder or those in whom the disorder is to be prevented. The disorder may result from any cause, including idiopathic, cardiotrophic, or myotrophic causes, or ischemia or ischemic insults, such as myocardial infarction.

"Chronic" administration refers to administration of the agent(s) in a continuous mode as opposed to an acute mode, so as to maintain the initial effect, such as an anti-hypertrophic effect, for an extended period of time.

"Mammal" for purposes of treatment refers to any animal classified as a mammal, including humans, domestic and farm animals, and zoo, sports, or pet animals, such as dogs, horses, cats, cows, sheep, pigs, etc. Preferably, the mammal is human.

Administration "in combination with" one or more further therapeutic agents includes simultaneous (concurrent) and consecutive administration in any order.

The phrase "cardiovascular, endothelial or angiogenic agents" refers generically to any drug that acts in treating cardiovascular, endothelial, and angiogenic disorders. Examples of cardiovascular agents are those that promote vascular homeostasis by modulating blood pressure, heart rate, heart contractility, and endothelial and smooth muscle biology, all of which factors have a role in cardiovascular disease. Specific examples of these include angiotensin-II receptor antagonists; endothelin receptor antagonists such as, for example, BOSENTAN™ and MOXONODIN™; interferon-gamma (IFN-γ); des-aspartate-angiotensin I; thrombolytic agents, *e.g.*, streptokinase, urokinase, t-PA, and a t-PA variant specifically designed to have longer half-life and very high fibrin specificity, TNK t-PA (a T103N, N117Q, KHRR(296-299)AAAA t-PA variant, Keyt *et al.*, Proc. Natl. Acad. Sci. USA, 91: 3670-3674 (1994)); inotropic or hypertensive agents such as digoxigenin and β-adrenergic receptor blocking agents, *e.g.*, propranolol, timolol, tertalolol, carteolol, nadolol, betaxolol, penbutolol, acetobutolol, atenolol, metoprolol, and carvedilol; angiotensin converting enzyme (ACE) inhibitors, *e.g.*, quinapril, captopril, enalapril, ramipril, benazepril, fosinopril, and lisinopril; diuretics, *e.g.*, chlorothiazide, hydrochlorothiazide, hydroflumethazide, methylchlorothiazide, benzthiazide, dichlorphenamide, acetazolamide, and indapamide; and calcium channel blockers, *e.g.*, diltiazem, nifedipine, verapamil, nicardipine. One preferred category of this type is a therapeutic agent used for the treatment of cardiac hypertrophy or of a physiological condition instrumental in the development of cardiac hypertrophy, such as elevated blood pressure, aortic stenosis, or myocardial infarction.

"Angiogenic agents" and "endothelial agents" are active agents that promote angiogenesis and/or endothelial cell growth, or, if applicable, vasculogenesis. This would include factors that accelerate wound healing, such as growth hormone, insulin-like growth factor-I (IGF-I), VEGF, VIGF, PDGF, epidermal growth factor (EGF), CTGF and members of its family, FGF, and TGF-α and TGF-β.

"Angiostatic agents" are active agents that inhibit angiogenesis or vasculogenesis or otherwise inhibit or prevent growth of cancer cells. Examples include antibodies or other antagonists to angiogenic agents as defined above, such as antibodies to VEGF. They additionally include cytotherapeutic agents such as cytotoxic agents, chemotherapeutic agents, growth-inhibitory agents, apoptotic agents, and other agents to treat cancer, such as anti-HER-2, anti-CD20, and other bioactive and organic chemical agents.

In a pharmacological sense, in the context of the present invention, a "therapeutically effective amount" of an active agent such as a PRO polypeptide or agonist or antagonist thereto or an anti-PRO antibody, refers to an amount effective in the treatment of a cardiovascular, endothelial or angiogenic disorder in a mammal and can be determined empirically.

As used herein, an "effective amount" of an active agent such as a PRO polypeptide or agonist or antagonist thereto or an anti-PRO antibody, refers to an amount effective for carrying out a stated purpose, wherein such amounts may be determined empirically for the desired effect.

The terms "PRO polypeptide" and "PRO" as used herein and when immediately followed by a numerical designation refer to various polypeptides, wherein the complete designation (*i.e.*, PRO/number) refers to specific polypeptide sequences as described herein. The terms "PRO/number polypeptide" and "PRO/number" wherein the term "number" is provided as an actual numerical designation as used herein encompass native sequence polypeptides and polypeptide variants (which are further defined herein). The PRO polypeptides described herein



may be isolated from a variety of sources, such as from human tissue types or from another source, or prepared by recombinant or synthetic methods.

5 A "native sequence PRO polypeptide" comprises a polypeptide having the same amino acid sequence as the corresponding PRO polypeptide derived from nature. Such native sequence PRO polypeptides can be isolated from nature or can be produced by recombinant or synthetic means. The term "native sequence PRO polypeptide" specifically encompasses naturally-occurring truncated or secreted forms of the specific PRO polypeptide (e.g., an extracellular domain sequence), naturally-occurring variant forms (e.g., alternatively spliced forms) and naturally-occurring allelic variants of the polypeptide. In various embodiments of the invention, the native sequence PRO polypeptides disclosed herein are mature or full-length native sequence polypeptides comprising the full-length amino acids sequences shown in the accompanying figures. Start and stop codons are shown in bold font and underlined in the figures. However, while the PRO polypeptide disclosed in the accompanying figures are shown to begin with methionine residues designated herein as amino acid position 1 in the figures, it is conceivable and possible that other methionine residues located either upstream or downstream from the amino acid position 1 in the figures may be employed as the starting amino acid residue for the PRO polypeptides.

15 The PRO polypeptide "extracellular domain" or "ECD" refers to a form of the PRO polypeptide which is essentially free of the transmembrane and cytoplasmic domains. Ordinarily, a PRO polypeptide ECD will have less than 1% of such transmembrane and/or cytoplasmic domains and preferably, will have less than 0.5% of such domains. It will be understood that any transmembrane domains identified for the PRO polypeptides of the present invention are identified pursuant to criteria routinely employed in the art for identifying that type of hydrophobic domain. The exact boundaries of a transmembrane domain may vary but most likely by no more than about 5 amino acids at either end of the domain as initially identified herein. Optionally, therefore, an extracellular domain of a PRO polypeptide may contain from about 5 or fewer amino acids on either side of the transmembrane domain/extracellular domain boundary as identified in the Examples or specification and such polypeptides, with or without the associated signal peptide, and nucleic acid encoding them, are contemplated by the present invention.

25 The approximate location of the "signal peptides" of the various PRO polypeptides disclosed herein are shown in the present specification and/or the accompanying figures. It is noted, however, that the C-terminal boundary of a signal peptide may vary, but most likely by no more than about 5 amino acids on either side of the signal peptide C-terminal boundary as initially identified herein, wherein the C-terminal boundary of the signal peptide may be identified pursuant to criteria routinely employed in the art for identifying that type of amino acid sequence element (e.g., Nielsen *et al.*, Prot. Eng., 10:1-6 (1997) and von Heinje *et al.*, Nucl. Acids Res., 14:4683-4690 (1986)). Moreover, it is also recognized that, in some cases, cleavage of a signal sequence from a secreted polypeptide is not entirely uniform, resulting in more than one secreted species. These mature polypeptides, where the signal peptide is cleaved within no more than about 5 amino acids on either side of the C-terminal boundary of the signal peptide as identified herein, and the polynucleotides encoding them, are contemplated by the present invention.

35 "PRO polypeptide variant" means an active PRO polypeptide as defined above or below having at least about 80% amino acid sequence identity with a full-length native sequence PRO polypeptide sequence as disclosed

herein, a PRO polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO polypeptide, with or without the signal peptide, as disclosed herein or any other fragment of a full-length PRO polypeptide sequence as disclosed herein. Such PRO polypeptide variants include, for instance, PRO polypeptides wherein one or more amino acid residues are added, or deleted, at the N- or C-terminus of the full-length native amino acid sequence. Ordinarily, a PRO polypeptide variant will have at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97% or 98% amino acid sequence identity and alternatively at least about 99% amino acid sequence identity to a full-length native sequence PRO polypeptide sequence as disclosed herein, a PRO polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO polypeptide, with or without the signal peptide, as disclosed herein or any other specifically defined fragment of a full-length PRO polypeptide sequence as disclosed herein. Ordinarily, PRO variant polypeptides are at least about 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 150 or 200 amino acids in length and alternatively at least about 300 amino acids in length, or more.

"Percent (%) amino acid sequence identity" with respect to the PRO polypeptide sequences identified herein is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in a PRO sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN, ALIGN-2 or Megalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full-length of the sequences being compared. For purposes herein, however, % amino acid sequence identity values are obtained as described below by using the sequence comparison computer program ALIGN-2, wherein the complete source code for the ALIGN-2 program is provided in Table 1. The ALIGN-2 sequence comparison computer program was authored by Genentech, Inc., and the source code shown in Table 1 has been filed with user documentation in the U.S. Copyright Office, Washington D.C., 20559, where it is registered under U.S. Copyright Registration No. TXU510087. The ALIGN-2 program is publicly available through Genentech, Inc., South San Francisco, California or may be compiled from the source code provided in Table 1. The ALIGN-2 program should be compiled for use on a UNIX operating system, preferably digital UNIX V4.0D. All sequence comparison parameters are set by the ALIGN-2 program and do not vary.

For purposes herein, the % amino acid sequence identity of a given amino acid sequence A to, with, or against a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has or comprises a certain % amino acid sequence identity to, with, or against a given amino acid sequence B) is calculated as follows:

$$100 \text{ times the fraction } X/Y$$

where X is the number of amino acid residues scored as identical matches by the sequence alignment program

ALIGN-2 in that program's alignment of A and B, and where Y is the total number of amino acid residues in B. It will be appreciated that where the length of amino acid sequence A is not equal to the length of amino acid sequence B, the % amino acid sequence identity of A to B will not equal the % amino acid sequence identity of B to A. As examples of % amino acid sequence identity calculations, Tables 2-3 demonstrate how to calculate the % amino acid sequence identity of the amino acid sequence designated "Comparison Protein" to the amino acid sequence designated "PRO".

Unless specifically stated otherwise, all % amino acid sequence identity values used herein are obtained as described above using the ALIGN-2 sequence comparison computer program. However, % amino acid sequence identity may also be determined using the sequence comparison program NCBI-BLAST2 (Altschul *et al.*, Nucleic Acids Res., 25:3389-3402 (1997)). The NCBI-BLAST2 sequence comparison program may be downloaded from <http://www.ncbi.nlm.nih.gov> or otherwise obtained from the National Institute of Health, Bethesda, MD. NCBI-BLAST2 uses several search parameters, wherein all of those search parameters are set to default values including, for example, unmask = yes, strand = all, expected occurrences = 10, minimum low complexity length = 15/5, multi-pass e-value = 0.01, constant for multi-pass = 25, dropoff for final gapped alignment = 25 and scoring matrix = BLOSUM62.

In situations where NCBI-BLAST2 is employed for amino acid sequence comparisons, the % amino acid sequence identity of a given amino acid sequence A to, with, or against a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has or comprises a certain % amino acid sequence identity to, with, or against a given amino acid sequence B) is calculated as follows:

$$100 \text{ times the fraction } X/Y$$

where X is the number of amino acid residues scored as identical matches by the sequence alignment program NCBI-BLAST2 in that program's alignment of A and B, and where Y is the total number of amino acid residues in B. It will be appreciated that where the length of amino acid sequence A is not equal to the length of amino acid sequence B, the % amino acid sequence identity of A to B will not equal the % amino acid sequence identity of B to A.

In addition, % amino acid sequence identity may also be determined using the WU-BLAST-2 computer program (Altschul *et al.*, Methods in Enzymology, 266:460-480 (1996)). Most of the WU-BLAST-2 search parameters are set to the default values. Those not set to default values, *i.e.*, the adjustable parameters, are set with the following values: overlap span = 1, overlap fraction = 0.125, word threshold (T) = 11, and scoring matrix = BLOSUM62. For purposes herein, a % amino acid sequence identity value is determined by dividing (a) the number of matching identical amino acids residues between the amino acid sequence of the PRO polypeptide of interest having a sequence derived from the native PRO polypeptide and the comparison amino acid sequence of interest (*i.e.*, the sequence against which the PRO polypeptide of interest is being compared which may be a PRO variant polypeptide) as determined by WU-BLAST-2 by (b) the total number of amino acid residues of the PRO polypeptide of interest. For example, in the statement "a polypeptide comprising an amino acid sequence A which

has or having at least 80% amino acid sequence identity to the amino acid sequence B", the amino acid sequence A is the comparison amino acid sequence of interest and the amino acid sequence B is the amino acid sequence of the PRO polypeptide of interest.

5 "PRO variant polynucleotide" or "PRO variant nucleic acid sequence" means a nucleic acid molecule which encodes an active PRO polypeptide as defined below and which has at least about 80% nucleic acid sequence identity with a nucleotide acid sequence encoding a full-length native sequence PRO polypeptide sequence as disclosed herein, a full-length native sequence PRO polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO polypeptide, with or without the signal peptide, as disclosed herein or any other fragment of a full-length PRO polypeptide sequence as disclosed herein. Ordinarily, a PRO variant  
10 polynucleotide will have at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97% or 98% nucleic acid sequence identity and alternatively at least about 99% nucleic acid sequence identity with a nucleic acid sequence encoding a full-length native sequence PRO polypeptide sequence as disclosed herein, a full-length native sequence PRO polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO polypeptide, with or without the signal sequence, as disclosed herein or  
15 any other fragment of a full-length PRO polypeptide sequence as disclosed herein. Variants do not encompass the native nucleotide sequence.

Ordinarily, PRO variant polynucleotides are at least about 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 450, or 600 nucleotides in length and alternatively at least about 900 nucleotides in length, or more.

20 "Percent (%) nucleic acid sequence identity" with respect to the PRO polypeptide-encoding nucleic acid sequences identified herein is defined as the percentage of nucleotides in a candidate sequence that are identical with the nucleotides in a PRO polypeptide-encoding nucleic acid sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity. Alignment for purposes of determining percent nucleic acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN, ALIGN-2 or Megalign  
25 (DNASTAR) software. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full-length of the sequences being compared. For purposes herein, however, % nucleic acid sequence identity values are obtained as described below by using the sequence comparison computer program ALIGN-2, wherein the complete source code for the ALIGN-2 program is provided in Table 1. The ALIGN-2 sequence comparison computer program was authored by  
30 Genentech, Inc., and the source code shown in Table 1 has been filed with user documentation in the U.S. Copyright Office, Washington D.C., 20559, where it is registered under U.S. Copyright Registration No. TXU510087. The ALIGN-2 program is publicly available through Genentech, Inc., South San Francisco, California or may be compiled from the source code provided in Table 1. The ALIGN-2 program should be compiled for use on a UNIX operating system, preferably digital UNIX V4.0D. All sequence comparison parameters are set by the ALIGN-2  
35 program and do not vary.

For purposes herein, the % nucleic acid sequence identity of a given nucleic acid sequence C to, with, or against a given nucleic acid sequence D (which can alternatively be phrased as a given nucleic acid sequence C that

has or comprises a certain % nucleic acid sequence identity to, with, or against a given nucleic acid sequence D) is calculated as follows:

$$100 \text{ times the fraction } W/Z$$

5

where W is the number of nucleotides scored as identical matches by the sequence alignment program ALIGN-2 in that program's alignment of C and D, and where Z is the total number of nucleotides in D. It will be appreciated that where the length of nucleic acid sequence C is not equal to the length of nucleic acid sequence D, the % nucleic acid sequence identity of C to D will not equal the % nucleic acid sequence identity of D to C. As examples of % nucleic acid sequence identity calculations, Tables 4-5 demonstrate how to calculate the % nucleic acid sequence identity of the nucleic acid sequence designated "Comparison DNA" to the nucleic acid sequence designated "PRO-DNA".

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Unless specifically stated otherwise, all % nucleic acid sequence identity values used herein are obtained as described above using the ALIGN-2 sequence comparison computer program. However, % nucleic acid sequence identity may also be determined using the sequence comparison program NCBI-BLAST2 (Altschul *et al.*, Nucleic Acids Res., 25:3389-3402 (1997)). The NCBI-BLAST2 sequence comparison program may be downloaded from <http://www.ncbi.nlm.nih.gov> or otherwise obtained from the National Institute of Health, Bethesda, MD. NCBI-BLAST2 uses several search parameters, wherein all of those search parameters are set to default values including, for example, unmask = yes, strand = all, expected occurrences = 10, minimum low complexity length = 15/5, multi-pass e-value = 0.01, constant for multi-pass = 25, dropoff for final gapped alignment = 25 and scoring matrix = BLOSUM62.

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In situations where NCBI-BLAST2 is employed for sequence comparisons, the % nucleic acid sequence identity of a given nucleic acid sequence C to, with, or against a given nucleic acid sequence D (which can alternatively be phrased as a given nucleic acid sequence C that has or comprises a certain % nucleic acid sequence identity to, with, or against a given nucleic acid sequence D) is calculated as follows:

25

$$100 \text{ times the fraction } W/Z$$

30

where W is the number of nucleotides scored as identical matches by the sequence alignment program NCBI-BLAST2 in that program's alignment of C and D, and where Z is the total number of nucleotides in D. It will be appreciated that where the length of nucleic acid sequence C is not equal to the length of nucleic acid sequence D, the % nucleic acid sequence identity of C to D will not equal the % nucleic acid sequence identity of D to C.

35

In addition, % nucleic acid sequence identity values may also be generated using the WU-BLAST-2 computer program (Altschul *et al.*, Methods in Enzymology, 266:460-480 (1996)). Most of the WU-BLAST-2 search parameters are set to the default values. Those not set to default values, *i.e.*, the adjustable parameters, are set with the following values: overlap span = 1, overlap fraction = 0.125, word threshold (T) = 11, and scoring matrix = BLOSUM62. For purposes herein, a % nucleic acid sequence identity value is determined by dividing (a)

the number of matching identical nucleotides between the nucleic acid sequence of the PRO polypeptide-encoding nucleic acid molecule of interest having a sequence derived from the native sequence PRO polypeptide-encoding nucleic acid and the comparison nucleic acid molecule of interest (*i.e.*, the sequence against which the PRO polypeptide-encoding nucleic acid molecule of interest is being compared which may be a variant PRO polynucleotide) as determined by WU-BLAST-2 by (b) the total number of nucleotides of the PRO polypeptide-encoding nucleic acid molecule of interest. For example, in the statement "an isolated nucleic acid molecule comprising a nucleic acid sequence A which has or having at least 80% nucleic acid sequence identity to the nucleic acid sequence B", the nucleic acid sequence A is the comparison nucleic acid molecule of interest and the nucleic acid sequence B is the nucleic acid sequence of the PRO polypeptide-encoding nucleic acid molecule of interest.

In other embodiments, PRO variant polynucleotides are nucleic acid molecules that encode an active PRO polypeptide and which are capable of hybridizing, preferably under stringent hybridization and wash conditions, to nucleotide sequences encoding the full-length PRO polypeptide as shown in the specification herein and accompanying figures. PRO variant polypeptides may be those that are encoded by a PRO variant polynucleotide.

"Isolated", when used to describe the various polypeptides disclosed herein, means a polypeptide that has been identified and separated and/or recovered from a component of its natural environment. Preferably, the isolated polypeptide is free of association with all components with which it is naturally associated. Contaminant components of its natural environment are materials that would typically interfere with diagnostic or therapeutic uses for the polypeptide, and may include enzymes, hormones, and other proteinaceous or non-proteinaceous solutes. In preferred embodiments, the polypeptide will be purified (1) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (2) to homogeneity by SDS-PAGE under non-reducing or reducing conditions using Coomassie blue or, preferably, silver stain. Isolated polypeptide includes polypeptide *in situ* within recombinant cells, since at least one component of the PRO natural environment will not be present. Ordinarily, however, isolated polypeptide will be prepared by at least one purification step.

An "isolated" nucleic acid molecule encoding a PRO polypeptide or an "isolated" nucleic acid molecule encoding an anti-PRO antibody is a nucleic acid molecule that is identified and separated from at least one contaminant nucleic acid molecule with which it is ordinarily associated in the natural source of the PRO-encoding nucleic acid or the natural source of the anti-PRO-encoding nucleic acid. Preferably, the isolated nucleic acid is free of association with all components with which it is naturally associated. An isolated PRO-encoding nucleic acid molecule or an isolated anti-PRO-encoding nucleic acid molecule is other than in the form or setting in which it is found in nature. Isolated nucleic acid molecules therefore are distinguished from the PRO-encoding nucleic acid molecule or from the anti-PRO-encoding nucleic acid molecule as it exists in natural cells. However, an isolated nucleic acid molecule encoding a PRO polypeptide or an isolated nucleic acid molecule encoding an anti-PRO antibody includes PRO-nucleic acid molecules or anti-PRO-nucleic acid molecules contained in cells that ordinarily express PRO polypeptides or anti-PRO antibodies where, for example, the nucleic acid molecule is in a chromosomal location different from that of natural cells.

The term "control sequences" refers to DNA sequences necessary for the expression of an operably linked

coding sequence in a particular host organism. The control sequences that are suitable for prokaryotes, for example, include a promoter, optionally an operator sequence, and a ribosome binding site. Eukaryotic cells are known to utilize, for example, promoters, polyadenylation signals, and enhancers.

Nucleic acid is "operably linked" when it is placed into a functional relationship with another nucleic acid sequence. For example, DNA for a presequence or secretory leader is operably linked to DNA for a PRO polypeptide if it is expressed as a preprotein that participates in the secretion of the polypeptide; a promoter or enhancer is operably linked to a coding sequence if it affects the transcription of the sequence; or a ribosome binding site is operably linked to a coding sequence if it is positioned so as to facilitate translation. Generally, "operably linked" means that the DNA sequences being linked are contiguous, and, in the case of a secretory leader, contiguous and in the same reading frame. However, enhancers do not have to be contiguous. Linking is accomplished by ligation at convenient restriction sites. If such sites do not exist, synthetic oligonucleotide adaptors or linkers are used in accordance with conventional practice.

"Stringency" of hybridization reactions is readily determinable by one of ordinary skill in the art, and generally is an empirical calculation dependent upon probe length, washing temperature, and salt concentration. In general, longer probes require higher temperatures for proper annealing, while shorter probes need lower temperatures. Hybridization generally depends on the ability of denatured DNA to reanneal when complementary strands are present in an environment below their melting temperature. The higher the degree of desired homology between the probe and hybridizable sequence, the higher the relative temperature that can be used. As a result, it follows that higher relative temperatures would tend to make the reaction conditions more stringent, while lower temperatures less so. For additional details and explanation of stringency of hybridization reactions, *see*, Ausubel *et al.*, Current Protocols in Molecular Biology (Wiley Interscience Publishers, 1995).

"Stringent conditions" or "high-stringency conditions", as defined herein, may be identified by those that: (1) employ low ionic strength and high temperature for washing, for example, 0.015 M sodium chloride/0.0015 M sodium citrate/0.1% sodium dodecyl sulfate at 50°C; (2) employ during hybridization a denaturing agent, such as formamide, for example, 50% (v/v) formamide with 0.1% bovine serum albumin/0.1% Ficoll/0.1% polyvinylpyrrolidone/50mM sodium phosphate buffer at pH 6.5 with 750 mM sodium chloride, 75 mM sodium citrate at 42°C; or (3) employ 50% formamide, 5 x SSC (0.75 M NaCl, 0.075 M sodium citrate), 50 mM sodium phosphate (pH 6.8), 0.1% sodium pyrophosphate, 5 x Denhardt's solution, sonicated salmon sperm DNA (50 µg/ml), 0.1% SDS, and 10% dextran sulfate at 42°C, with washes at 42°C in 0.2 x SSC (sodium chloride/sodium citrate) and 50% formamide at 55°C, followed by a high-stringency wash consisting of 0.1 x SSC containing EDTA at 55°C.

"Moderately-stringent conditions" may be identified as described by Sambrook *et al.*, Molecular Cloning: A Laboratory Manual (New York: Cold Spring Harbor Press, 1989), and include the use of washing solution and hybridization conditions (*e.g.*, temperature, ionic strength, and % SDS) less stringent than those described above. An example of moderately stringent conditions is overnight incubation at 37°C in a solution comprising: 20% formamide, 5 x SSC (150 mM NaCl, 15 mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5 x Denhardt's solution, 10% dextran sulfate, and 20 mg/ml denatured sheared salmon sperm DNA, followed by washing the filters

in 1 x SSC at about 37-50°C. The skilled artisan will recognize how to adjust the temperature, ionic strength, etc. as necessary to accommodate factors such as probe length and the like.

The modifier "epitope-tagged" when used herein refers to a chimeric polypeptide comprising a PRO polypeptide fused to a "tag polypeptide". The tag polypeptide has enough residues to provide an epitope against which an antibody can be made, yet is short enough such that it does not interfere with activity of the polypeptide to which it is fused. The tag polypeptide preferably also is fairly unique so that the antibody does not substantially cross-react with other epitopes. Suitable tag polypeptides generally have at least six amino acid residues and usually between about 8 and 50 amino acid residues (preferably, between about 10 and 20 amino acid residues).

"Active" or "activity" in the context of PRO variants refers to form(s) of PRO proteins that retain the biologic and/or immunologic activities of a native or naturally-occurring PRO polypeptide.

"Biological activity" in the context of a molecule that antagonizes a PRO polypeptide that can be identified by the screening assays disclosed herein (e.g., an organic or inorganic small molecule, peptide, etc.) is used to refer to the ability of such molecules to bind or complex with the PRO polypeptide identified herein, or otherwise interfere with the interaction of the PRO polypeptide with other cellular proteins or otherwise inhibits the transcription or translation of the PRO polypeptide. Particularly preferred biological activity includes cardiac hypertrophy, activity that acts on systemic disorders that affect vessels, such as diabetes mellitus, as well as diseases of the arteries, capillaries, veins, and/or lymphatics, and cancer.

The term "antagonist" is used in the broadest sense, and includes any molecule that partially or fully blocks, inhibits, or neutralizes one or more of the biological activities of a native PRO polypeptide disclosed herein, for example, if applicable, its mitogenic or angiogenic activity. Antagonists of a PRO polypeptide may act by interfering with the binding of a PRO polypeptide to a cellular receptor, by incapacitating or killing cells that have been activated by a PRO polypeptide, or by interfering with vascular endothelial cell activation after binding of a PRO polypeptide to a cellular receptor. All such points of intervention by a PRO polypeptide antagonist shall be considered equivalent for purposes of this invention. The antagonists inhibit the mitogenic, angiogenic, or other biological activity of PRO polypeptides, and thus are useful for the treatment of diseases or disorders characterized by undesirable excessive neovascularization, including by way of example tumors, and especially solid malignant tumors, rheumatoid arthritis, psoriasis, atherosclerosis, diabetic and other retinopathies, retrolental fibroplasia, age-related macular degeneration, neovascular glaucoma, hemangiomas, thyroid hyperplasias (including Grave's disease), corneal and other tissue transplantation, and chronic inflammation. The antagonists also are useful for the treatment of diseases or disorders characterized by undesirable excessive vascular permeability, such as edema associated with brain tumors, ascites associated with malignancies, Meigs' syndrome, lung inflammation, nephrotic syndrome, pericardial effusion (such as that associated with pericarditis), and pleural effusion. In a similar manner, the term "agonist" is used in the broadest sense and includes any molecule that mimics a biological activity of a native PRO polypeptide disclosed herein. Suitable agonist or antagonist molecules specifically include agonist or antagonist antibodies or antibody fragments, fragments, or amino acid sequence variants of native PRO polypeptides, peptides, small organic molecules, etc.

A "small molecule" is defined herein to have a molecular weight below about 500 daltons.



The term "PRO polypeptide receptor" as used herein refers to a cellular receptor for a PRO polypeptide, ordinarily a cell-surface receptor found on vascular endothelial cells, as well as variants thereof that retain the ability to bind a PRO polypeptide.

5 "Antibodies" (Abs) and "immunoglobulins" (Igs) are glycoproteins having the same structural characteristics. While antibodies exhibit binding specificity to a specific antigen, immunoglobulins include both antibodies and other antibody-like molecules that lack antigen specificity. Polypeptides of the latter kind are, for example, produced at low levels by the lymph system and at increased levels by myelomas. The term "antibody" is used in the broadest sense and specifically covers, without limitation, intact monoclonal antibodies, polyclonal antibodies, multispecific antibodies (*e.g.*, bispecific antibodies) formed from at least two intact antibodies, and  
10 antibody fragments, so long as they exhibit the desired biological activity.

"Native antibodies" and "native immunoglobulins" are usually heterotetrameric glycoproteins of about 150,000 daltons, composed of two identical light (L) chains and two identical heavy (H) chains. Each light chain is linked to a heavy chain by one covalent disulfide bond, while the number of disulfide linkages varies among the heavy chains of different immunoglobulin isotypes. Each heavy and light chain also has regularly spaced intrachain  
15 disulfide bridges. Each heavy chain has at one end a variable domain ( $V_H$ ) followed by a number of constant domains. Each light chain has a variable domain at one end ( $V_L$ ) and a constant domain at its other end; the constant domain of the light chain is aligned with the first constant domain of the heavy chain, and the light-chain variable domain is aligned with the variable domain of the heavy chain. Particular amino acid residues are believed to form an interface between the light- and heavy-chain variable domains.

20 The term "variable" refers to the fact that certain portions of the variable domains differ extensively in sequence among antibodies and are used in the binding and specificity of each particular antibody to and for its particular antigen. However, the variability is not evenly distributed throughout the variable domains of antibodies. It is concentrated in three segments called complementarity-determining regions (CDRs) or hypervariable regions both in the light-chain and the heavy-chain variable domains. The more highly conserved portions of variable  
25 domains are called the framework regions (FR). The variable domains of native heavy and light chains each comprise four FR regions, largely adopting a  $\beta$ -sheet configuration, connected by three CDRs, which form loops connecting, and in some cases forming part of, the  $\beta$ -sheet structure. The CDRs in each chain are held together in close proximity by the FR regions and, with the CDRs from the other chain, contribute to the formation of the antigen-binding site of antibodies. See, Kabat *et al.*, NIH Publ. No.91-3242, Vol. I, pages 647-669 (1991). The  
30 constant domains are not involved directly in binding an antibody to an antigen, but exhibit various effector functions, such as participation of the antibody in antibody-dependent cellular toxicity.

"Antibody fragments" comprise a portion of an intact antibody, preferably the antigen-binding or variable region of the intact antibody. Examples of antibody fragments include Fab, Fab', F(ab')<sub>2</sub>, and Fv fragments; diabodies; linear antibodies (Zapata *et al.*, Protein Eng., 8(10): 1057-1062 (1995)); single-chain antibody molecules; and multispecific antibodies formed from antibody fragments.  
35

Papain digestion of antibodies produces two identical antigen-binding fragments, called "Fab" fragments, each with a single antigen-binding site, and a residual "Fc" fragment, whose name reflects its ability to crystallize

readily. Pepsin treatment yields an  $F(ab')_2$  fragment that has two antigen-combining sites and is still capable of cross-linking antigen.

"Fv" is the minimum antibody fragment that contains a complete antigen-recognition and -binding site. This region consists of a dimer of one heavy- and one light-chain variable domain in tight, non-covalent association. It is in this configuration that the three CDRs of each variable domain interact to define an antigen-binding site on the surface of the  $V_H$ - $V_L$  dimer. Collectively, the six CDRs confer antigen-binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDRs specific for an antigen) has the ability to recognize and bind antigen, although at a lower affinity than the entire binding site.

The Fab fragment also contains the constant domain of the light chain and the first constant domain (CH1) of the heavy chain. Fab' fragments differ from Fab fragments by the addition of a few residues at the carboxy terminus of the heavy chain CH1 domain including one or more cysteines from the antibody hinge region. Fab'-SH is the designation herein for Fab' in which the cysteine residue(s) of the constant domains bear a free thiol group.  $F(ab')_2$  antibody fragments originally were produced as pairs of Fab' fragments that have hinge cysteines between them. Other chemical couplings of antibody fragments are also known.

The "light chains" of antibodies (immunoglobulins) from any vertebrate species can be assigned to one of two clearly distinct types, called kappa ( $\kappa$ ) and lambda ( $\lambda$ ), based on the amino acid sequences of their constant domains.

Depending on the amino acid sequence of the constant domain of their heavy chains, immunoglobulins can be assigned to different classes. There are five major classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM; and several of these may be further divided into subclasses (isotypes), e.g., IgG1, IgG2, IgG3, IgG4, IgA, and IgA2. The heavy-chain constant domains that correspond to the different classes of immunoglobulins are called  $\alpha$ ,  $\delta$ ,  $\epsilon$ ,  $\gamma$ , and  $\mu$ , respectively. The subunit structures and three-dimensional configurations of different classes of immunoglobulins are well known.

The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally-occurring mutations that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site. Furthermore, in contrast to conventional (polyclonal) antibody preparations that typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen. In addition to their specificity, the monoclonal antibodies are advantageous in that they are synthesized by the hybridoma culture, uncontaminated by other immunoglobulins. The modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. For example, the monoclonal antibodies to be used in accordance with the present invention may be made by the hybridoma method first described by Kohler *et al.*, Nature, 256: 495 (1975), or may be made by recombinant DNA methods (see, e.g., U.S. Patent No. 4,816,567). The "monoclonal antibodies" may also be isolated from phage antibody libraries using the techniques described in Clackson *et al.*, Nature, 352: 624-628 (1991) and Marks *et al.*, J. Mol. Biol., 222: 581-597 (1991), for example.

The monoclonal antibodies herein specifically include "chimeric" antibodies (immunoglobulins) in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity. U.S. Patent No. 4,816,567; Morrison *et al.*, Proc. Natl. Acad. Sci. USA, **81**: 6851-6855 (1984).

"Humanized" forms of non-human (e.g., murine) antibodies are chimeric immunoglobulins, immunoglobulin chains, or fragments thereof (such as Fv, Fab, Fab', F(ab')<sub>2</sub>, or other antigen-binding subsequences of antibodies) that contain minimal sequence derived from non-human immunoglobulin. For the most part, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a CDR of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat or rabbit having the desired specificity, affinity, and capacity. In some instances, Fv FR residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, humanized antibodies may comprise residues that are found neither in the recipient antibody nor in the imported CDR or framework sequences. These modifications are made to further refine and maximize antibody performance. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin sequence. The humanized antibody preferably also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. For further details, see Jones *et al.*, Nature, **321**: 522-525 (1986); Reichmann *et al.*, Nature, **332**: 323-329 (1988); and Presta, Curr. Op. Struct. Biol., **2**: 593-596 (1992). The humanized antibody includes a PRIMATIZED™ antibody wherein the antigen-binding region of the antibody is derived from an antibody produced by immunizing macaque monkeys with the antigen of interest.

"Single-chain Fv" or "sFv" antibody fragments comprise the V<sub>H</sub> and V<sub>L</sub> domains of an antibody, wherein these domains are present in a single polypeptide chain. Preferably, the Fv polypeptide further comprises a polypeptide linker between the V<sub>H</sub> and V<sub>L</sub> domains that enables the sFv to form the desired structure for antigen binding. For a review of sFv see, Pluckthun in The Pharmacology of Monoclonal Antibodies, Vol. 113, Rosenberg and Moore, eds. (Springer-Verlag: New York, 1994), pp. 269-315.

The term "diabodies" refers to small antibody fragments with two antigen-binding sites, which fragments comprise a heavy-chain variable domain (V<sub>H</sub>) connected to a light-chain variable domain (V<sub>L</sub>) in the same polypeptide chain (V<sub>H</sub> - V<sub>L</sub>). By using a linker that is too short to allow pairing between the two domains on the same chain, the domains are forced to pair with the complementary domains of another chain and create two antigen-binding sites. Diabodies are described more fully in, for example, EP 404,097; WO 93/11161; and Hollinger *et al.*, Proc. Natl. Acad. Sci. USA, **90**: 6444-6448 (1993).

An "isolated" antibody is one that has been identified and separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials that would interfere

with diagnostic or therapeutic uses for the antibody, and may include enzymes, hormones, and other proteinaceous or nonproteinaceous solutes. In preferred embodiments, the antibody will be purified (1) to greater than 95% by weight of antibody as determined by the Lowry method, and most preferably more than 99% by weight, (2) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (3) to homogeneity by SDS-PAGE under reducing or nonreducing conditions using Coomassie blue or, preferably, silver stain. Isolated antibody includes the antibody *in situ* within recombinant cells, since at least one component of the antibody's natural environment will not be present. Ordinarily, however, isolated antibody will be prepared by at least one purification step.

An antibody that "specifically binds to" or is "specific for" a particular polypeptide or an epitope on a particular polypeptide is one that binds to that particular polypeptide or epitope on a particular polypeptide without substantially binding to any other polypeptide or polypeptide epitope.

The word "label" when used herein refers to a detectable compound or other composition that is conjugated directly or indirectly to the antibody so as to generate a "labeled" antibody. The label may be detectable by itself (e.g., radioisotope labels or fluorescent labels) or, in the case of an enzymatic label, may catalyze chemical alteration of a substrate compound or composition that is detectable. Radionuclides that can serve as detectable labels include, for example, I-131, I-123, I-125, Y-90, Re-188, At-211, Cu-67, Bi-212, and Pd-109. The label may also be a non-detectable entity such as a toxin.

By "solid phase" is meant a non-aqueous matrix to which an antibody of the present invention can adhere. Examples of solid phases encompassed herein include those formed partially or entirely of glass (e.g., controlled pore glass), polysaccharides (e.g., agarose), polyacrylamides, polystyrene, polyvinyl alcohol and silicones. In certain embodiments, depending on the context, the solid phase can comprise the well of an assay plate; in others it is a purification column (e.g., an affinity chromatography column). This term also includes a discontinuous solid phase of discrete particles, such as those described in U.S. Patent No. 4,275,149.

A "liposome" is a small vesicle composed of various types of lipids, phospholipids and/or surfactant that is useful for delivery of a drug (such as the PRO polypeptide or antibodies thereto disclosed herein) to a mammal. The components of the liposome are commonly arranged in a bilayer formation, similar to the lipid arrangement of biological membranes.

As used herein, the term "immunoadhesin" designates antibody-like molecules that combine the binding specificity of a heterologous protein (an "adhesin") with the effector functions of immunoglobulin constant domains. Structurally, the immunoadhesins comprise a fusion of an amino acid sequence with the desired binding specificity that is other than the antigen recognition and binding site of an antibody (i.e., is "heterologous"), and an immunoglobulin constant domain sequence. The adhesin part of an immunoadhesin molecule typically is a contiguous amino acid sequence comprising at least the binding site of a receptor or a ligand. The immunoglobulin constant domain sequence in the immunoadhesin may be obtained from any immunoglobulin, such as IgG-1, IgG-2, IgG-3, or IgG-4 subtypes, IgA (including IgA-1 and IgA-2), IgE, IgD, or IgM.

As shown below, Table 1 provides the complete source code for the ALIGN-2 sequence comparison computer program. This source code may be routinely compiled for use on a UNIX operating system to provide

the ALIGN-2 sequence comparison computer program.

5 In addition, Tables 2-5 show hypothetical exemplifications for using the below described method to determine % amino acid sequence identity (Tables 2-3) and % nucleic acid sequence identity (Tables 4-5) using the ALIGN-2 sequence comparison computer program, wherein "PRO" represents the amino acid sequence of a hypothetical PRO polypeptide of interest, "Comparison Protein" represents the amino acid sequence of a polypeptide against which the "PRO" polypeptide of interest is being compared, "PRO-DNA" represents a hypothetical PRO-encoding nucleic acid sequence of interest, "Comparison DNA" represents the nucleotide sequence of a nucleic acid molecule against which the "PRO-DNA" nucleic acid molecule of interest is being compared, "X", "Y", and "Z" each represent different hypothetical amino acid residues and "N", "L" and "V" each represent different hypothetical nucleotides.

10

Table 1

```

/*
 *
 * C-C increased from 12 to 15
 * Z is average of EQ
 * B is average of ND
 * match with stop is _M; stop-stop = 0; J (joker) match = 0
 */
#define _M      -8      /* value of a match with a stop */

int _day[26][26] = {
/* A B C D E F G H I J K L M N O P Q R S T U V W X Y Z */
/* A */ { 2, 0, -2, 0, 0, -4, 1, -1, -1, 0, -1, -2, -1, 0, _M, 1, 0, -2, 1, 1, 0, 0, -6, 0, -3, 0},
/* B */ { 0, 3, -4, 3, 2, -5, 0, 1, -2, 0, 0, -3, -2, 2, _M, -1, 1, 0, 0, 0, 0, -2, -5, 0, -3, 1},
/* C */ {-2, -4, 15, -5, -5, -4, -3, -3, -2, 0, -5, -6, -5, -4, _M, -3, -5, -4, 0, -2, 0, -2, -8, 0, 0, -5},
/* D */ { 0, 3, -5, 4, 3, -6, 1, 1, -2, 0, 0, -4, -3, 2, _M, -1, 2, -1, 0, 0, 0, -2, -7, 0, -4, 2},
/* E */ { 0, 2, -5, 3, 4, -5, 0, 1, -2, 0, 0, -3, -2, 1, _M, -1, 2, -1, 0, 0, 0, -2, -7, 0, -4, 3},
/* F */ {-4, -5, -4, -6, -5, 9, -5, -2, 1, 0, -5, 2, 0, -4, _M, -5, -5, -4, -3, -3, 0, -1, 0, 0, 7, -5},
/* G */ { 1, 0, -3, 1, 0, -5, 5, -2, -3, 0, -2, -4, -3, 0, _M, -1, -1, -3, 1, 0, 0, -1, -7, 0, -5, 0},
/* H */ {-1, 1, -3, 1, 1, -2, -2, 6, -2, 0, 0, -2, -2, 2, _M, 0, 3, 2, -1, -1, 0, -2, -3, 0, 0, 2},
/* I */ {-1, -2, -2, -2, -2, 1, -3, -2, 5, 0, -2, 2, 2, -2, _M, -2, -2, -2, -1, 0, 0, 4, -5, 0, -1, -2},
/* J */ { 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, _M, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0},
/* K */ {-1, 0, -5, 0, 0, -5, -2, 0, -2, 0, 5, -3, 0, 1, _M, -1, 1, 3, 0, 0, 0, -2, -3, 0, -4, 0},
/* L */ {-2, -3, -6, -4, -3, 2, -4, -2, 2, 0, -3, 6, 4, -3, _M, -3, -2, -3, -3, -1, 0, 2, -2, 0, -1, -2},
/* M */ {-1, -2, -5, -3, -2, 0, -3, -2, 2, 0, 0, 4, 6, -2, _M, -2, -1, 0, -2, -1, 0, 2, -4, 0, -2, -1},
/* N */ { 0, 2, -4, 2, 1, -4, 0, 2, -2, 0, 1, -3, -2, 2, _M, -1, 1, 0, 1, 0, 0, -2, -4, 0, -2, 1},
/* O */ { _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, 0, _M, _M, _M, _M, _M, _M, _M, _M, _M},
/* P */ { 1, -1, -3, -1, -1, -5, -1, 0, -2, 0, -1, -3, -2, -1, _M, 6, 0, 0, 1, 0, 0, -1, -6, 0, -5, 0},
/* Q */ { 0, 1, -5, 2, 2, -5, -1, 3, -2, 0, 1, -2, -1, 1, _M, 0, 4, 1, -1, -1, 0, -2, -5, 0, -4, 3},
/* R */ {-2, 0, -4, -1, -1, -4, -3, 2, -2, 0, 3, -3, 0, 0, _M, 0, 1, 6, 0, -1, 0, -2, 2, 0, -4, 0},
/* S */ { 1, 0, 0, 0, 0, -3, 1, -1, -1, 0, 0, -3, -2, 1, _M, 1, -1, 0, 2, 1, 0, -1, -2, 0, -3, 0},
/* T */ { 1, 0, -2, 0, 0, -3, 0, -1, 0, 0, 0, -1, -1, 0, _M, 0, -1, -1, 1, 3, 0, 0, -5, 0, -3, 0},
/* U */ { 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, _M, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0},
/* V */ { 0, -2, -2, -2, -2, -1, -1, -2, 4, 0, -2, 2, 2, -2, _M, -1, -2, -2, -1, 0, 0, 4, -6, 0, -2, -2},
/* W */ {-6, -5, -8, -7, -7, 0, -7, -3, -5, 0, -3, -2, -4, -4, _M, -6, -5, 2, -2, -5, 0, -6, 17, 0, 0, -6},
/* X */ { 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, _M, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0},
/* Y */ {-3, -3, 0, -4, -4, 7, -5, 0, -1, 0, -4, -1, -2, -2, _M, -5, -4, -4, -3, -3, 0, -2, 0, 0, 10, -4},
/* Z */ { 0, 1, -5, 2, 3, -5, 0, 2, -2, 0, 0, -2, -1, 1, _M, 0, 3, 0, 0, 0, 0, -2, -6, 0, -4, 4}
};

```

**Table 1 (cont')**

```

/*
 */
#include <stdio.h>
#include <ctype.h>

#define MAXJMP      16      /* max jumps in a diag */
#define MAXGAP      24      /* don't continue to penalize gaps larger than this */
#define JMPS        1024    /* max jmps in an path */
#define MX          4       /* save if there's at least MX-1 bases since last jmp */

#define DMAT        3       /* value of matching bases */
#define DMIS        0       /* penalty for mismatched bases */
#define DINS0       8       /* penalty for a gap */
#define DINS1       1       /* penalty per base */
#define PINS0       8       /* penalty for a gap */
#define PINS1       4       /* penalty per residue */

struct jmp {
    short          n[MAXJMP]; /* size of jmp (neg for dely) */
    unsigned short x[MAXJMP]; /* base no. of jmp in seq x */
}; /* limits seq to 2^16 -1 */

struct diag {
    int            score;      /* score at last jmp */
    long           offset;     /* offset of prev block */
    short          ijmp;       /* current jmp index */
    struct jmp     jp;         /* list of jmps */
};

struct path {
    int            spc;        /* number of leading spaces */
    short          n[JMPS];    /* size of jmp (gap) */
    int            x[JMPS];    /* loc of jmp (last elem before gap) */
};

char              *ofile;     /* output file name */
char              *namex[2];  /* seq names: getseqs( ) */
char              *prog;      /* prog name for err msgs */
char              *seqx[2];   /* seqs: getseqs( ) */
int               dmax;       /* best diag: nw( ) */
int               dmax0;      /* final diag */
int               dna;        /* set if dna: main( ) */
int               endgaps;    /* set if penalizing end gaps */
int               gapx, gapy; /* total gaps in seqs */
int               len0, len1; /* seq lens */
int               ngapx, ngapy; /* total size of gaps */
int               smax;       /* max score: nw( ) */
int               *xbm;       /* bitmap for matching */
long              offset;     /* current offset in jmp file */
struct            diag        *dx; /* holds diagonals */
struct            path        pp[2]; /* holds path for seqs */

char              *calloc( ), *malloc( ), *index( ), *strcpy( );
char              *getseq( ), *g_calloc( );

```

**Table 1 (cont')**

```

/* Needleman-Wunsch alignment program
*
* usage: progs file1 file2
* where file1 and file2 are two dna or two protein sequences.
* The sequences can be in upper- or lower-case and may contain ambiguity
* Any lines beginning with ';', '>' or '<' are ignored
* Max file length is 65535 (limited by unsigned short x in the jmp struct)
* A sequence with 1/3 or more of its elements ACGTU is assumed to be DNA
* Output is in the file "align.out"
*
* The program may create a tmp file in /tmp to hold info about traceback.
* Original version developed under BSD 4.3 on a vax 8650.
*/
#include "nw.h"
#include "day.h"

static  _dbval[26] = {
1,14,2,13,0,0,4,11,0,0,12,0,3,15,0,0,0,5,6,8,8,7,9,0,10,0
};

static  _pbval[26] = {
1, 2|(1<<('D'-'A'))|(1<<('N'-'A')), 4, 8, 16, 32, 64,
128, 256, 0xFFFFFFF, 1<<10, 1<<11, 1<<12, 1<<13, 1<<14,
1<<15, 1<<16, 1<<17, 1<<18, 1<<19, 1<<20, 1<<21, 1<<22,
1<<23, 1<<24, 1<<25|(1<<('E'-'A'))|(1<<('Q'-'A'))
};

main(ac, av)
int      ac;
char     *av[];
{
    prog = av[0];
    if (ac != 3) {
        fprintf(stderr, "usage: %s file1 file2\n", prog);
        fprintf(stderr, "where file1 and file2 are two dna or two protein sequences.\n");
        fprintf(stderr, "The sequences can be in upper- or lower-case\n");
        fprintf(stderr, "Any lines beginning with ';', '>' or '<' are ignored\n");
        fprintf(stderr, "Output is in the file \"align.out\"\n");
        exit(1);
    }
    namex[0] = av[1];
    namex[1] = av[2];
    seqx[0] = getseq(namex[0], &len0);
    seqx[1] = getseq(namex[1], &len1);
    xbm = (dna)? _dbval : _pbval;

    endgaps = 0;                /* 1 to penalize endgaps */
    ofile = "align.out";        /* output file */

    nw();                       /* fill in the matrix, get the possible jmps */
    readjmps();                 /* get the actual jmps */
    print();                    /* print stats, alignment */

    cleanup(0);                 /* unlink any tmp files */
}

```

**main**



**Table 1 (cont')**

```

/* do the alignment, return best score: main( )
 * dna: values in Fitch and Smith, PNAS, 80, 1382-1386, 1983
 * pro: PAM 250 values
 * When scores are equal, we prefer mismatches to any gap, prefer
 * a new gap to extending an ongoing gap, and prefer a gap in seqx
 * to a gap in seq y.
 */
nw( )
{
    char          *px, *py;          /* seqs and ptrs */
    int            *ndely, *dely;     /* keep track of dely */
    int            ndelx, delx;       /* keep track of delx */
    int            *tmp;              /* for swapping row0, row1 */
    int            mis;               /* score for each type */
    int            ins0, ins1;        /* insertion penalties */
    register       id;                /* diagonal index */
    register       ij;               /* jmp index */
    register       *col0, *col1;      /* score for curr, last row */
    register       xx, yy;            /* index into seqs */

    dx = (struct diag *)g_calloc("to get diags", len0+len1+1, sizeof(struct diag));

    ndely = (int *)g_calloc("to get ndely", len1+1, sizeof(int));
    dely = (int *)g_calloc("to get dely", len1+1, sizeof(int));
    col0 = (int *)g_calloc("to get col0", len1+1, sizeof(int));
    col1 = (int *)g_calloc("to get col1", len1+1, sizeof(int));
    ins0 = (dna)? DINS0 : PINS0;
    ins1 = (dna)? DINS1 : PINS1;

    smax = -10000;
    if (endgaps) {
        for (col0[0] = dely[0] = -ins0, yy = 1; yy <= len1; yy++) {
            col0[yy] = dely[yy] = col0[yy-1] - ins1;
            ndely[yy] = yy;
        }
        col0[0] = 0;          /* Waterman Bull Math Biol 84 */
    }
    else
        for (yy = 1; yy <= len1; yy++)
            dely[yy] = -ins0;

    /* fill in match matrix
     */
    for (px = seqx[0], xx = 1; xx <= len0; px++, xx++) {
        /* initialize first entry in col
         */
        if (endgaps) {
            if (xx == 1)
                col1[0] = delx = -(ins0+ins1);
            else
                col1[0] = delx = col0[0] - ins1;
            ndelx = xx;
        }
        else {
            col1[0] = 0;
            delx = -ins0;
            ndelx = 0;
        }
    }
}

```

nw

Table 1 (cont')

...NW

```

for (py = seqx[1], yy = 1; yy <= len1; py++, yy++) {
    mis = col0[yy-1];
    if (dna)
        mis += (xbm[*px-'A']&xbm[*py-'A'])? DMAT : DMIS;
    else
        mis += _day[*px-'A'][*py-'A'];

    /* update penalty for del in x seq;
     * favor new del over ongong del
     * ignore MAXGAP if weighting endgaps
     */
    if (endgaps || ndely[yy] < MAXGAP) {
        if (col0[yy] - ins0 >= dely[yy]) {
            dely[yy] = col0[yy] - (ins0+ins1);
            ndely[yy] = 1;
        } else {
            dely[yy] -= ins1;
            ndely[yy]++;
        }
    } else {
        if (col0[yy] - (ins0+ins1) >= dely[yy]) {
            dely[yy] = col0[yy] - (ins0+ins1);
            ndely[yy] = 1;
        } else
            ndely[yy]++;
    }

    /* update penalty for del in y seq;
     * favor new del over ongong del
     */
    if (endgaps || ndelx < MAXGAP) {
        if (col1[yy-1] - ins0 >= delx) {
            delx = col1[yy-1] - (ins0+ins1);
            ndelx = 1;
        } else {
            delx -= ins1;
            ndelx++;
        }
    } else {
        if (col1[yy-1] - (ins0+ins1) >= delx) {
            delx = col1[yy-1] - (ins0+ins1);
            ndelx = 1;
        } else
            ndelx++;
    }

    /* pick the maximum score; we're favoring
     * mis over any del and delx over dely
     */

```

**Table 1 (cont')**

...nw

```

id = xx - yy + len1 - 1;
if (mis >= delx && mis >= dely[yy])
    coll[yy] = mis;
else if (delx >= dely[yy]) {
    coll[yy] = delx;
    ij = dx[id].ijmp;
    if (dx[id].jp.n[0] && (!dna || (ndelx >= MAXJMP
    && xx > dx[id].jp.x[ij]+MX) || mis > dx[id].score+DINS0)) {
        dx[id].ijmp++;
        if (++ij >= MAXJMP) {
            writejumps(id);
            ij = dx[id].ijmp = 0;
            dx[id].offset = offset;
            offset += sizeof(struct jmp) + sizeof(offset);
        }
        dx[id].jp.n[ij] = ndelx;
        dx[id].jp.x[ij] = xx;
        dx[id].score = delx;
    }
    else {
        coll[yy] = dely[yy];
        ij = dx[id].ijmp;
        if (dx[id].jp.n[0] && (!dna || (ndely[yy] >= MAXJMP
        && xx > dx[id].jp.x[ij]+MX) || mis > dx[id].score+DINS0)) {
            dx[id].ijmp++;
            if (++ij >= MAXJMP) {
                writejumps(id);
                ij = dx[id].ijmp = 0;
                dx[id].offset = offset;
                offset += sizeof(struct jmp) + sizeof(offset);
            }
            dx[id].jp.n[ij] = -ndely[yy];
            dx[id].jp.x[ij] = xx;
            dx[id].score = dely[yy];
        }
        if (xx == len0 && yy < len1) {
            /* last col
            */
            if (endgaps)
                coll[yy] -= ins0+ins1*(len1-yy);
            if (coll[yy] > smax) {
                smax = coll[yy];
                dmax = id;
            }
        }
    }
}
if (endgaps && xx < len0)
    coll[yy-1] -= ins0+ins1*(len0-xx);
if (coll[yy-1] > smax) {
    smax = coll[yy-1];
    dmax = id;
}
tmp = col0; col0 = coll; coll = tmp;
}
(void) free((char *)ndely);
(void) free((char *)dely);
(void) free((char *)col0);
(void) free((char *)coll);
}

```

**Table 1 (cont')**

```

/*
 *
 * print() - only routine visible outside this module
 *
 * static:
 * getmat() - trace back best path, count matches: print()
 * pr_align() - print alignment of described in array p[]: print()
 * dumpblock() - dump a block of lines with numbers, stars: pr_align()
 * nums() - put out a number line: dumpblock()
 * putline() - put out a line (name, [num], seq, [num]): dumpblock()
 * stars() - put a line of stars: dumpblock()
 * stripname() - strip any path and prefix from a seqname
 */

#include "nw.h"

#define SPC      3
#define P_LINE  256    /* maximum output line */
#define P_SPC    3      /* space between name or num and seq */

extern _day[26][26];
int olen;              /* set output line length */
FILE *fx;              /* output file */

print()
{
    int    lx, ly, firstgap, lastgap;    /* overlap */

    if ((fx = fopen(ofile, "w")) == 0) {
        fprintf(stderr, "%s: can't write %s\n", prog, ofile);
        cleanup(1);
    }
    fprintf(fx, "< first sequence: %s (length = %d)\n", namex[0], len0);
    fprintf(fx, "< second sequence: %s (length = %d)\n", namex[1], len1);
    olen = 60;
    lx = len0;
    ly = len1;
    firstgap = lastgap = 0;
    if (dmax < len1 - 1) { /* leading gap in x */
        pp[0].spc = firstgap = len1 - dmax - 1;
        ly -= pp[0].spc;
    }
    else if (dmax > len1 - 1) { /* leading gap in y */
        pp[1].spc = firstgap = dmax - (len1 - 1);
        lx -= pp[1].spc;
    }
    if (dmax0 < len0 - 1) { /* trailing gap in x */
        lastgap = len0 - dmax0 - 1;
        lx -= lastgap;
    }
    else if (dmax0 > len0 - 1) { /* trailing gap in y */
        lastgap = dmax0 - (len0 - 1);
        ly -= lastgap;
    }
    getmat(lx, ly, firstgap, lastgap);
    pr_align();
}

```

**print**

Table 1 (cont')

```

/*
 * trace back the best path, count matches
 */
static
getmat(lx, ly, firstgap, lastgap)                                getmat
{
    int      lx, ly; /* "core" (minus endgaps) */
    int      firstgap, lastgap; /* leading trailing overlap */

    int      nm, i0, i1, siz0, siz1;
    char      outx[32];
    double    pct;
    register  n0, n1;
    register char *p0, *p1;

    /* get total matches, score
     */
    i0 = i1 = siz0 = siz1 = 0;
    p0 = seqx[0] + pp[1].spc;
    p1 = seqx[1] + pp[0].spc;
    n0 = pp[1].spc + 1;
    n1 = pp[0].spc + 1;

    nm = 0;
    while ( *p0 && *p1 ) {
        if (siz0) {
            p1++;
            n1++;
            siz0--;
        }
        else if (siz1) {
            p0++;
            n0++;
            siz1--;
        }
        else {
            if (xbm[*p0-'A']&xbm[*p1-'A'])
                nm++;
            if (n0++ == pp[0].x[i0])
                siz0 = pp[0].n[i0++];
            if (n1++ == pp[1].x[i1])
                siz1 = pp[1].n[i1++];
            p0++;
            p1++;
        }
    }

    /* pct homology:
     * if penalizing endgaps, base is the shorter seq
     * else, knock off overhangs and take shorter core
     */
    if (endgaps)
        lx = (len0 < len1)? len0 : len1;
    else
        lx = (lx < ly)? lx : ly;
    pct = 100.*(double)nm/(double)lx;
    fprintf(fx, "\n");
    fprintf(fx, "< %d match%s in an overlap of %d: %.2f percent similarity\n",
        nm, (nm == 1)? "" : "es", lx, pct);

```

**Table 1 (cont')**

```

fprintf(fx, "<gaps in first sequence: %d", gapx);
if (gapx) {
    (void) sprintf(outx, " (%d %s%s)",
        ngapx, (dna)? "base": "residue", (ngapx == 1)? "": "s");
    fprintf(fx, "%s", outx);

    fprintf(fx, ", gaps in second sequence: %d", gapy);
    if (gapy) {
        (void) sprintf(outx, " (%d %s%s)",
            ngapy, (dna)? "base": "residue", (ngapy == 1)? "": "s");
        fprintf(fx, "%s", outx);
    }
    if (dna)
        fprintf(fx,
            "\n<score: %d (match = %d, mismatch = %d, gap penalty = %d + %d per base)\n",
            smax, DMAT, DMIS, DINS0, DINS1);
    else
        fprintf(fx,
            "\n<score: %d (Dayhoff PAM 250 matrix, gap penalty = %d + %d per residue)\n",
            smax, PINS0, PINS1);
    if (endgaps)
        fprintf(fx,
            "<endgaps penalized. left endgap: %d %s%s, right endgap: %d %s%s\n",
            firstgap, (dna)? "base": "residue", (firstgap == 1)? "": "s",
            lastgap, (dna)? "base": "residue", (lastgap == 1)? "": "s");
    else
        fprintf(fx, "<endgaps not penalized\n");
}

static      nm;           /* matches in core -- for checking */
static      lmax;         /* lengths of stripped file names */
static      ij[2];        /* jmp index for a path */
static      nc[2];        /* number at start of current line */
static      ni[2];        /* current elem number -- for gapping */
static      siz[2];
static char *ps[2];        /* ptr to current element */
static char *po[2];        /* ptr to next output char slot */
static char out[2][P_LINE]; /* output line */
static char star[P_LINE];  /* set by stars() */

/*
 * print alignment of described in struct path pp[]
 */
static
pr_align()
{
    int      nm;           /* char count */
    int      more;
    register i;

    for (i = 0, lmax = 0; i < 2; i++) {
        nm = stripname(namex[i]);
        if (nm > lmax)
            lmax = nm;

        nc[i] = 1;
        ni[i] = 1;
        siz[i] = ij[i] = 0;
        ps[i] = seqx[i];
        po[i] = out[i];
    }
}

```

...getmat

pr\_align

Table 1 (cont')

...pr\_align

```

for (nn = nm = 0, more = 1; more;) {
    for (i = more = 0; i < 2; i++) {
        /*
         * do we have more of this sequence?
         */
        if (!*ps[i])
            continue;

        more++;

        if (pp[i].spc) { /* leading space */
            *po[i]++ = ' ';
            pp[i].spc--;
        }
        else if (siz[i]) { /* in a gap */
            *po[i]++ = '-';
            siz[i]--;
        }
        else { /* we're putting a seq element
                */
            *po[i] = *ps[i];
            if (islower(*ps[i]))
                *ps[i] = toupper(*ps[i]);
            po[i]++;
            ps[i]++;

            /*
             * are we at next gap for this seq?
             */
            if (ni[i] == pp[i].x[ij[i]]) {
                /*
                 * we need to merge all gaps
                 * at this location
                 */
                siz[i] = pp[i].n[ij[i]] + +;
                while (ni[i] == pp[i].x[ij[i]])
                    siz[i] += pp[i].n[ij[i]] + +;
            }
            ni[i]++;
        }
    }
    if (++nn == olen || !more && nn) {
        dumpblock();
        for (i = 0; i < 2; i++)
            po[i] = out[i];
        nn = 0;
    }
}

/*
 * dump a block of lines, including numbers, stars: pr_align( )
 */
static
dumpblock( )
{
    register i;

    for (i = 0; i < 2; i++)
        *po[i]-- = '\0';
}

```

dumpblock

Table 1 (cont')

...dumpblock

```

(void) putc('\n', fx);
for (i = 0; i < 2; i++) {
    if (*out[i] && (*out[i] != ' ' || *(po[i]) != ' ')) {
        if (i == 0)
            nums(i);
        if (i == 0 && *out[1])
            stars( );
        putline(i);
        if (i == 0 && *out[1])
            fprintf(fx, star);
        if (i == 1)
            nums(i);
    }
}

/*
 * put out a number line: dumpblock( )
 */
static
nums(ix)
int    ix;    /* index in out[] holding seq line */
{
    char    nline[P_LINE];
    register i, j;
    register char    *pn, *px, *py;

    for (pn = nline, i = 0; i < lmax+P_SPC; i++, pn++)
        *pn = ' ';
    for (i = nc[ix], py = out[ix]; *py; py++, pn++) {
        if (*py == ' ' || *py == '-')
            *pn = ' ';
        else {
            if (i%10 == 0 || (i == 1 && nc[ix] != 1)) {
                j = (i < 0)? -i : i;
                for (px = pn; j /= 10, px--)
                    *px = j%10 + '0';
                if (i < 0)
                    *px = '-';
            }
            else
                *pn = ' ';
            i++;
        }
    }
    *pn = '\0';
    nc[ix] = i;
    for (pn = nline; *pn; pn++)
        (void) putc(*pn, fx);
    (void) putc('\n', fx);
}

/*
 * put out a line (name, [num], seq, [num]): dumpblock( )
 */
static
putline(ix)
int    ix;
{

```

nums

putline



Table 1 (cont')

...putline

```

int          i;
register char *px;

for (px = namex[ix], i = 0; *px && *px != ':'; px++, i++)
    (void) putc(*px, fx);
for (; i < lmax+P_SPC; i++)
    (void) putc(' ', fx);

/* these count from 1:
 * ni[] is current element (from 1)
 * nc[] is number at start of current line
 */
for (px = out[ix]; *px; px++)
    (void) putc(*px&0x7F, fx);
(void) putc('\n', fx);
}

/*
 * put a line of stars (seqs always in out[0], out[1]): dumpblock( )
 */
static
stars()
{
    int          i;
    register char *p0, *p1, cx, *px;

    if (!*out[0] || (*out[0] == ' ' && *(p0[0]) == ' ') ||
        !*out[1] || (*out[1] == ' ' && *(p0[1]) == ' '))
        return;
    px = star;
    for (i = lmax+P_SPC; i; i--)
        *px++ = ' ';

    for (p0 = out[0], p1 = out[1]; *p0 && *p1; p0++, p1++) {
        if (isalpha(*p0) && isalpha(*p1)) {
            if (xbm[*p0-'A']&xbm[*p1-'A']) {
                cx = '*';
                nm++;
            }
            else if (!dna && day[*p0-'A'][*p1-'A'] > 0)
                cx = '.';
            else
                cx = ' ';
        }
        else
            cx = ' ';
        *px++ = cx;
    }
    *px++ = '\n';
    *px = '\0';
}

```

stars

**Table 1 (cont')**

```

/*
 * strip path or prefix from pn, return len: pr_align( )
 */
static
stripname(pn)
    char    *pn;    /* file name (may be path) */
{
    register char    *px, *py;

    py = 0;
    for (px = pn; *px; px++)
        if (*px == '/')
            py = px + 1;
    if (py)
        (void) strcpy(pn, py);
    return(strlen(pn));
}

```

**stripname**

**Table 1 (cont')**

```

/*
 * cleanup() -- cleanup any tmp file
 * getseq() -- read in seq, set dna, len, maxlen
 * g_calloc() -- calloc() with error checkin
 * readjumps() -- get the good jumps, from tmp file if necessary
 * writejumps() -- write a filled array of jumps to a tmp file: nw()
 */
#include "nw.h"
#include <sys/file.h>

char    *jname = "/tmp/homgXXXXXXX";      /* tmp file for jumps */
FILE    *fj;

int      cleanup( );                      /* cleanup tmp file */
long     lseek( );

/*
 * remove any tmp file if we blow
 */
cleanup(i)                                cleanup
{
    int    i;
    if (fj)
        (void) unlink(jname);
    exit(i);
}

/*
 * read, return ptr to seq, set dna, len, maxlen
 * skip lines starting with ';', '<', or '>'
 * seq in upper or lower case
 */
char    *
getseq(file, len)                          getseq
{
    char    *file;    /* file name */
    int      *len;    /* seq len */

    char    line[1024], *pseq;
    register char    *px, *py;
    int      natgc, tlen;
    FILE    *fp;

    if ((fp = fopen(file, "r")) == 0) {
        fprintf(stderr, "%s: can't read %s\n", prog, file);
        exit(1);
    }
    tlen = natgc = 0;
    while (fgets(line, 1024, fp)) {
        if (*line == ';' || *line == '<' || *line == '>')
            continue;
        for (px = line; *px != '\n'; px++)
            if (isupper(*px) || islower(*px))
                tlen++;
    }
    if ((pseq = malloc((unsigned)(tlen+6))) == 0) {
        fprintf(stderr, "%s: malloc() failed to get %d bytes for %s\n", prog, tlen+6, file);
        exit(1);
    }
    pseq[0] = pseq[1] = pseq[2] = pseq[3] = '\0';

```

**Table 1 (cont')**

...getseq

```

py = pseq + 4;
*len = tlen;
rewind(fp);

while (fgets(line, 1024, fp)) {
    if (*line == ';' || *line == '<' || *line == '>')
        continue;
    for (px = line; *px != '\n'; px++) {
        if (isupper(*px))
            *py++ = *px;
        else if (islower(*px))
            *py++ = toupper(*px);
        if (index("ATGCU", *(py-1)))
            natgc++;
    }
    *py++ = '\0';
    *py = '\0';
    (void) fclose(fp);
    dna = natgc > (tlen/3);
    return(pseq+4);
}

char *
g_calloc(msg, nx, sz)
char *msg;          /* program, calling routine */
int nx, sz;          /* number and size of elements */
{
    char *px, *calloc();

    if ((px = calloc((unsigned)nx, (unsigned)sz)) == 0) {
        if (*msg) {
            fprintf(stderr, "%s: g_calloc() failed %s (n=%d, sz=%d)\n", prog, msg, nx, sz);
            exit(1);
        }
    }
    return(px);
}

/*
 * get final jmps from dx[] or tmp file, set pp[], reset dmax: main()
 */
readjmps()
{
    int fd = -1;
    int siz, i0, i1;
    register i, j, xx;

    if (fj) {
        (void) fclose(fj);
        if ((fd = open(jname, O_RDONLY, 0)) < 0) {
            fprintf(stderr, "%s: can't open( ) %s\n", prog, jname);
            cleanup(1);
        }
    }
    for (i = i0 = i1 = 0, dmax0 = dmax, xx = len0; i++) {
        while (1) {
            for (j = dx[dmax].ijmp; j >= 0 && dx[dmax].jp.x[j] >= xx; j--)

```

g\_calloc

readjmps

**Table 1 (cont')****...readjumps**

```

    if (j < 0 && dx[dmax].offset && fj) {
        (void) lseek(fd, dx[dmax].offset, 0);
        (void) read(fd, (char *)&dx[dmax].jp, sizeof(struct jmp));
        (void) read(fd, (char *)&dx[dmax].offset, sizeof(dx[dmax].offset));
        dx[dmax].ijmp = MAXJMP-1;
    }
    else
        break;
}
if (i >= JMPS) {
    fprintf(stderr, "%s: too many gaps in alignment\n", prog);
    cleanup(1);
}
if (j >= 0) {
    siz = dx[dmax].jp.n[j];
    xx = dx[dmax].jp.x[j];
    dmax += siz;
    if (siz < 0) { /* gap in second seq */
        pp[1].n[i1] = -siz;
        xx += siz;
        /* id = xx - yy + len1 - 1
        */
        pp[1].x[i1] = xx - dmax + len1 - 1;
        gapy++;
        ngapy -= siz;
        /* ignore MAXGAP when doing endgaps */
        siz = (-siz < MAXGAP || endgaps)? -siz : MAXGAP;
        i1++;
    }
    else if (siz > 0) { /* gap in first seq */
        pp[0].n[i0] = siz;
        pp[0].x[i0] = xx;
        gapx++;
        ngapx += siz;
        /* ignore MAXGAP when doing endgaps */
        siz = (siz < MAXGAP || endgaps)? siz : MAXGAP;
        i0++;
    }
}
else
    break;
}

/* reverse the order of jumps
*/
for (j = 0, i0--; j < i0; j++, i0--) {
    i = pp[0].n[j]; pp[0].n[j] = pp[0].n[i0]; pp[0].n[i0] = i;
    i = pp[0].x[j]; pp[0].x[j] = pp[0].x[i0]; pp[0].x[i0] = i;
}
for (j = 0, i1--; j < i1; j++, i1--) {
    i = pp[1].n[j]; pp[1].n[j] = pp[1].n[i1]; pp[1].n[i1] = i;
    i = pp[1].x[j]; pp[1].x[j] = pp[1].x[i1]; pp[1].x[i1] = i;
}
if (fd >= 0)
    (void) close(fd);
if (fj) {
    (void) unlink(jname);
    fj = 0;
    offset = 0;
}

```

**Table 1 (cont')**

```

/*
 * write a filled jmp struct offset of the prev one (if any): nw( )
 */
writejumps(ix)                                writejumps
{
    int    ix;
    char    *mktemp( );

    if (!fj) {
        if (mktemp(jname) < 0) {
            fprintf(stderr, "%s: can't mktemp( ) %s\n", prog, jname);
            cleanup(1);
        }
        if ((fj = fopen(jname, "w")) == 0) {
            fprintf(stderr, "%s: can't write %s\n", prog, jname);
            exit(1);
        }
    }
    (void) fwrite((char *)&dx[ix].jp, sizeof(struct jmp), 1, fj);
    (void) fwrite((char *)&dx[ix].offset, sizeof(dx[ix].offset), 1, fj);
}

```

Table 2

|                    |                    |                           |
|--------------------|--------------------|---------------------------|
| PRO                | XXXXXXXXXXXXXXXXXX | (Length = 15 amino acids) |
| Comparison Protein | XXXXXXXXYYYYYY     | (Length = 12 amino acids) |

5 % amino acid sequence identity =  
 (the number of identically matching amino acid residues between the two polypeptide sequences as determined by  
 ALIGN-2) divided by (the total number of amino acid residues of the PRO polypeptide) =  
 5 divided by 15 = 33.3%

Table 3

|                    |                  |                           |
|--------------------|------------------|---------------------------|
| PRO                | XXXXXXXXXXXX     | (Length = 10 amino acids) |
| Comparison Protein | XXXXXXXXYYYYZZYZ | (Length = 15 amino acids) |

10 % amino acid sequence identity =  
 (the number of identically matching amino acid residues between the two polypeptide sequences as determined by  
 ALIGN-2) divided by (the total number of amino acid residues of the PRO polypeptide) =  
 5 divided by 10 = 50%

Table 4

|                |                |                           |
|----------------|----------------|---------------------------|
| PRO-DNA        | NNNNNNNNNNNNNN | (Length = 14 nucleotides) |
| Comparison DNA | NNNNNNLLLLLLLL | (Length = 16 nucleotides) |

10 % nucleic acid sequence identity =  
 (the number of identically matching nucleotides between the two nucleic acid sequences as determined by ALIGN-  
 2) divided by (the total number of nucleotides of the PRO-DNA nucleic acid sequence) =  
 6 divided by 14 = 42.9%

Table 5

|                |              |                           |
|----------------|--------------|---------------------------|
| PRO-DNA        | NNNNNNNNNNNN | (Length = 12 nucleotides) |
| Comparison DNA | NNNNLLLVV    | (Length = 9 nucleotides)  |

0 % nucleic acid sequence identity =  
 (the number of identically matching nucleotides between the two nucleic acid sequences as determined by ALIGN-  
 2) divided by (the total number of nucleotides of the PRO-DNA nucleic acid sequence) =  
 5 4 divided by 12 = 33.3%

## 5.2. Compositions and Methods of the Invention

### 5.2.1. PRO Variants

5 In addition to the full-length native sequence PRO polypeptides described herein, it is contemplated that PRO variants can be prepared. PRO variants can be prepared by introducing appropriate nucleotide changes into the PRO DNA, and/or by synthesis of the desired PRO polypeptide. Those skilled in the art will appreciate that amino acid changes may alter post-translational processes of the PRO polypeptide such as changing the number or position of glycosylation sites or altering the membrane anchoring characteristics.

10 Variations in the native full-length sequence PRO polypeptide or in various domains of the PRO polypeptide described herein, can be made, for example, using any of the techniques and guidelines for conservative and non-conservative mutations set forth, for instance, in U.S. Patent No. 5,364,934. Variations may be a substitution, deletion or insertion of one or more codons encoding the PRO polypeptide that results in a change in the amino acid sequence of the PRO polypeptide as compared with the native sequence PRO polypeptide. Optionally the variation is by substitution of at least one amino acid with any other amino acid in one or more of the domains of the PRO polypeptide. Guidance in determining which amino acid residue may be inserted, substituted or deleted without adversely affecting the desired activity may be found by comparing the sequence of the PRO polypeptide with that of homologous known protein molecules and minimizing the number of amino acid sequence changes made in regions of high homology. Amino acid substitutions can be the result of replacing one amino acid with another amino acid having similar structural and/or chemical properties, such as the replacement of a leucine with a serine, *i.e.*, conservative amino acid replacements. Insertions or deletions may optionally be in the range of about 15 1 to 5 amino acids. The variation allowed may be determined by systematically making insertions, deletions or substitutions of amino acids in the sequence and testing the resulting variants for activity exhibited by the full-length or mature native sequence.

20 In particular embodiments, conservative substitutions of interest are shown in Table 6 under the heading of preferred substitutions. If such substitutions result in a change in biological activity, then more substantial changes, denominated exemplary substitutions in Table 6, or as further described below in reference to amino acid classes, are introduced and the products screened.

25



Table 6

|    | Original<br>Residue | Exemplary<br>Substitutions             | Preferred<br>Substitutions |
|----|---------------------|--|----------------------------|
| 5  | Ala (A)             | val; leu; ile                          | val                        |
|    | Arg (R)             | lys; gln; asn                          | lys                        |
|    | Asn (N)             | gln; his; lys; arg                     | gln                        |
|    | Asp (D)             | glu                                    | glu                        |
|    | Cys (C)             | ser                                    | ser                        |
| 10 | Gln (Q)             | asn                                    | asn                        |
|    | Glu (E)             | asp                                    | asp                        |
|    | Gly (G)             | pro; ala                               | ala                        |
|    | His (H)             | asn; gln; lys; arg                     | arg                        |
|    | Ile (I)             | leu; val; met; ala; phe;<br>norleucine | leu                        |
| 15 | Leu (L)             | norleucine; ile; val;<br>met; ala; phe | ile                        |
|    | Lys (K)             | arg; gln; asn                          | arg                        |
|    | Met (M)             | leu; phe; ile                          | leu                        |
|    | Phe (F)             | leu; val; ile; ala; tyr                | leu                        |
|    | Pro (P)             | ala                                    | ala                        |
| 20 | Ser (S)             | thr                                    | thr                        |
|    | Thr (T)             | ser                                    | ser                        |
|    | Trp (W)             | tyr; phe                               | tyr                        |
|    | Tyr (Y)             | trp; phe; thr; ser                     | phe                        |
|    | Val (V)             | ile; leu; met; phe;<br>ala; norleucine | leu                        |

Substantial modifications in function or immunological identity of the PRO polypeptide are accomplished by selecting substitutions that differ significantly in their effect on maintaining (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a sheet or helical conformation, (b) the charge or hydrophobicity of the molecule at the target site, or (c) the bulk of the side chain. Naturally occurring residues are divided into groups based on common side-chain properties:

- (1) hydrophobic: norleucine, met, ala, val, leu, ile;
- (2) neutral hydrophilic: cys, ser, thr;
- (3) acidic: asp, glu;
- (4) basic: asn, gln, his, lys, arg;
- (5) residues that influence chain orientation: gly, pro; and
- (6) aromatic: trp, tyr, phe.

Non-conservative substitutions will entail exchanging a member of one of these classes for another class. Such substituted residues also may be introduced into the conservative substitution sites or, more preferably, into the remaining (non-conserved) sites.

The variations can be made using methods known in the art such as oligonucleotide-mediated (site-directed) mutagenesis, alanine scanning, and PCR mutagenesis. Site-directed mutagenesis [Carter *et al.*, Nucl. Acids Res., 13:4331 (1986); Zoller *et al.*, Nucl. Acids Res., 10:6487 (1987)], cassette mutagenesis [Wells *et al.*, Gene, 34:315 (1985)], restriction selection mutagenesis [Wells *et al.*, Philos. Trans. R. Soc. London SerA, 317:415

(1986)] or other known techniques can be performed on the cloned DNA to produce the PRO variant DNA.

Scanning amino acid analysis can also be employed to identify one or more amino acids along a contiguous sequence. Among the preferred scanning amino acids are relatively small, neutral amino acids. Such amino acids include alanine, glycine, serine, and cysteine. Alanine is typically a preferred scanning amino acid among this group because it eliminates the side-chain beyond the beta-carbon and is less likely to alter the main-chain conformation of the variant [Cunningham and Wells, Science, 244: 1081-1085 (1989)]. Alanine is also typically preferred because it is the most common amino acid. Further, it is frequently found in both buried and exposed positions [Creighton, The Proteins, (W.H. Freeman & Co., N.Y.); Chothia, J. Mol. Biol., 150:1 (1976)]. If alanine substitution does not yield adequate amounts of variant, an isoteric amino acid can be used.

#### 5.2.2. Modifications of PRO Polypeptides

Covalent modifications of PRO polypeptides are included within the scope of this invention. One type of covalent modification includes reacting targeted amino acid residues of a PRO polypeptide with an organic derivatizing agent that is capable of reacting with selected side chains or the N- or C- terminal residues of the PRO polypeptide. Derivatization with bifunctional agents is useful, for instance, for crosslinking the PRO polypeptide to a water-insoluble support matrix or surface for use in the method for purifying anti-PRO antibodies, and vice-versa. Commonly used crosslinking agents include, e.g., 1,1-bis(diazoacetyl)-2-phenylethane, glutaraldehyde, N-hydroxysuccinimide esters, for example, esters with 4-azidosalicylic acid, homobifunctional imidoesters, including disuccinimidyl esters such as 3,3'-dithiobis(succinimidylpropionate), bifunctional maleimides such as bis-N-maleimido-1,8-octane and agents such as methyl-3-[(p-azidophenyl)dithio]propioimide.

Other modifications include deamidation of glutamyl and asparaginy residues to the corresponding glutamyl and aspartyl residues, respectively, hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl or threonyl residues, methylation of the  $\alpha$ -amino groups of lysine, arginine, and histidine side chains [T.E. Creighton, Proteins: Structure and Molecular Properties, W.H. Freeman & Co., San Francisco, pp. 79-86 (1983)], acetylation of the N-terminal amine, and amidation of any C-terminal carboxyl group.

Another type of covalent modification of the PRO polypeptide included within the scope of this invention comprises altering the native glycosylation pattern of the polypeptide. "Altering the native glycosylation pattern" is intended for purposes herein to mean deleting one or more carbohydrate moieties found in the native sequence PRO polypeptide (either by removing the underlying glycosylation site or by deleting the glycosylation by chemical and/or enzymatic means), and/or adding one or more glycosylation sites that are not present in the native sequence PRO polypeptide. In addition, the phrase includes qualitative changes in the glycosylation of the native proteins, involving a change in the nature and proportions of the various carbohydrate moieties present.

Addition of glycosylation sites to the PRO polypeptide may be accomplished by altering the amino acid sequence. The alteration may be made, for example, by the addition of, or substitution by, one or more serine or threonine residues to the native sequence PRO polypeptide (for O-linked glycosylation sites). The PRO amino acid sequence may optionally be altered through changes at the DNA level, particularly by mutating the DNA encoding the PRO polypeptide at preselected bases such that codons are generated that will translate into the desired amino

acids.

Another means of increasing the number of carbohydrate moieties on the PRO polypeptide is by chemical or enzymatic coupling of glycosides to the polypeptide. Such methods are described in the art, *e.g.*, in WO 87/05330 published 11 September 1987, and in Aplin and Wriston, CRC Crit. Rev. Biochem., pp. 259-306 (1981).

Removal of carbohydrate moieties present on the PRO polypeptide may be accomplished chemically or enzymatically or by mutational substitution of codons encoding for amino acid residues that serve as targets for glycosylation. Chemical deglycosylation techniques are known in the art and described, for instance, by Hakimuddin, *et al.*, Arch. Biochem. Biophys., 259:52 (1987) and by Edge *et al.*, Anal. Biochem., 118:131 (1981). Enzymatic cleavage of carbohydrate moieties on polypeptides can be achieved by the use of a variety of endo- and exo-glycosidases as described by Thotakura *et al.*, Meth. Enzymol., 138:350 (1987).

Another type of covalent modification of the PRO polypeptide comprises linking the PRO polypeptide to one of a variety of nonproteinaceous polymers, *e.g.*, polyethylene glycol (PEG), polypropylene glycol, or polyoxyalkylenes, in the manner set forth in U.S. Patent Nos. 4,640,835; 4,496,689; 4,301,144; 4,670,417; 4,791,192 or 4,179,337.

The PRO polypeptide of the present invention may also be modified in a way to form a chimeric molecule comprising the PRO polypeptide fused to another, heterologous polypeptide or amino acid sequence.

In one embodiment, such a chimeric molecule comprises a fusion of the PRO polypeptide with a protein transduction domain which targets the PRO polypeptide for delivery to various tissues and more particularly across the brain blood barrier, using, for example, the protein transduction domain of human immunodeficiency virus TAT protein (Schwarze *et al.*, 1999, *Science* 285: 1569-72).

In another embodiment, such a chimeric molecule comprises a fusion of the PRO polypeptide with a tag polypeptide which provides an epitope to which an anti-tag antibody can selectively bind. The epitope tag is generally placed at the amino- or carboxyl- terminus of the PRO polypeptide. The presence of such epitope-tagged forms of the PRO polypeptide can be detected using an antibody against the tag polypeptide. Also, provision of the epitope tag enables the PRO polypeptide to be readily purified by affinity purification using an anti-tag antibody or another type of affinity matrix that binds to the epitope tag. Various tag polypeptides and their respective antibodies are well known in the art. Examples include poly-histidine (poly-His) or poly-histidine-glycine (poly-His-gly) tags; the flu HA tag polypeptide and its antibody 12CA5 [Field *et al.*, Mol. Cell. Biol., 8:2159-2165 (1988)]; the c-myc tag and the 8F9, 3C7, 6E10, G4, B7 and 9E10 antibodies thereto [Evan *et al.*, Molecular and Cellular Biology, 5:3610-3616 (1985)]; and the Herpes Simplex virus glycoprotein D (gD) tag and its antibody [Paborsky *et al.*, Protein Engineering, 3(6):547-553 (1990)]. Other tag polypeptides include the Flag-peptide [Hopp *et al.*, BioTechnology, 6:1204-1210 (1988)]; the KT3 epitope peptide [Martin *et al.*, Science, 255:192-194 (1992)]; an  $\alpha$ -tubulin epitope peptide [Skinner *et al.*, J. Biol. Chem., 266:15163-15166 (1991)]; and the T7 gene 10 protein peptide tag [Lutz-Freyermuth *et al.*, Proc. Natl. Acad. Sci. USA, 87:6393-6397 (1990)].

In an alternative embodiment, the chimeric molecule may comprise a fusion of the PRO polypeptide with an immunoglobulin or a particular region of an immunoglobulin. For a bivalent form of the chimeric molecule (also referred to as an "immunoadhesin"), such a fusion could be to the Fc region of an IgG molecule. The Ig fusions

preferably include the substitution of a soluble (transmembrane domain deleted or inactivated) form of a PRO polypeptide in place of at least one variable region within an Ig molecule. In a particularly preferred embodiment, the immunoglobulin fusion includes the hinge, CH2 and CH3, or the hinge, CH1, CH2 and CH3 regions of an IgG1 molecule. For the production of immunoglobulin fusions *see* also, U.S. Patent No. 5,428,130 issued June 27, 1995.

5

### 5.2.3. Preparation of the PRO Polypeptide

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO polypeptides. In particular, cDNAs encoding PRO polypeptides have been identified and isolated, as disclosed in further detail in the Examples below. It is noted that proteins produced in separate expression rounds may be given different PRO numbers but the UNQ number is unique for any given DNA and the encoded protein, and will not be changed. However, for sake of simplicity, in the present specification the protein encoded by the PRO DNA as well as all further native homologues and variants included in the foregoing definition of PRO polypeptides, will be referred to as "PRO" regardless of their origin or mode of preparation.

The description below relates primarily to production of PRO polypeptides by culturing cells transformed or transfected with a vector containing nucleic acid encoding PRO polypeptides. It is, of course, contemplated that alternative methods that are well known in the art may be employed to prepare the PRO polypeptide. For instance, the PRO polypeptide sequence, or portions thereof, may be produced by direct peptide synthesis using solid-phase techniques. *See, e.g., Stewart et al., Solid-Phase Peptide Synthesis* (W.H. Freeman Co.: San Francisco, CA, 1969); Merrifield, *J. Am. Chem. Soc.*, **85**: 2149-2154 (1963). *In vitro* protein synthesis may be performed using manual techniques or by automation. Automated synthesis may be accomplished, for instance, with an Applied Biosystems Peptide Synthesizer (Foster City, CA) using manufacturer's instructions. Various portions of the PRO polypeptide may be chemically synthesized separately and combined using chemical or enzymatic methods to produce the full-length PRO polypeptide.

#### 5.2.3.1. Isolation of DNA Encoding PRO Polypeptides

DNA encoding the PRO polypeptide may be obtained from a cDNA library prepared from tissue believed to possess the mRNA encoding the PRO polypeptide and to express it at a detectable level. Accordingly, DNAs encoding the human PRO polypeptide can be conveniently obtained from cDNA libraries prepared from human tissues, such as described in the Examples. The gene encoding the PRO polypeptide may also be obtained from a genomic library or by oligonucleotide synthesis.

Libraries can be screened with probes (such as antibodies to the PRO polypeptide or oligonucleotides of at least about 20-80 bases) designed to identify the gene of interest or the protein encoded by it. Screening the cDNA or genomic library with the selected probe may be conducted using standard procedures, such as described in Sambrook *et al., supra*. An alternative means to isolate the gene encoding the PRO polypeptide is to use PCR methodology. Sambrook *et al., supra*; Dieffenbach *et al., PCR Primer: A Laboratory Manual* (New York: Cold

Spring Harbor Laboratory Press, 1995).

The Examples below describe techniques for screening a cDNA library. The oligonucleotide sequences selected as probes should be of sufficient length and sufficiently unambiguous that false positives are minimized. The oligonucleotide is preferably labeled such that it can be detected upon hybridization to DNA in the library being screened. Methods of labeling are well known in the art, and include the use of radiolabels like <sup>32</sup>P-labeled ATP, biotinylation, or enzyme labeling. Hybridization conditions, including moderate stringency and high stringency, are provided in Sambrook *et al.*, *supra*.

Sequences identified in such library screening methods can be compared and aligned to other known sequences deposited and available in public databases such as GenBank or other private sequence databases. Sequence identity (at either the amino acid or nucleotide level) within defined regions of the molecule or across the full-length sequence can be determined through sequence alignment using computer software programs such as ALIGN, DNASTar, and INHERIT, which employ various algorithms to measure homology.

Nucleic acid having protein coding sequence may be obtained by screening selected cDNA or genomic libraries using the deduced amino acid sequence disclosed herein for the first time, and, if necessary, using conventional primer extension procedures as described in Sambrook *et al.*, *supra*, to detect precursors and processing intermediates of mRNA that may not have been reverse-transcribed into cDNA.

#### 5.2.3.2. Selection and Transformation of Host Cells

Host cells are transfected or transformed with expression or cloning vectors described herein for PRO polypeptide production and cultured in conventional nutrient media modified as appropriate for inducing promoters, selecting transformants, or amplifying the genes encoding the desired sequences. The culture conditions, such as media, temperature, pH, and the like, can be selected by the skilled artisan without undue experimentation. In general, principles, protocols, and practical techniques for maximizing the productivity of cell cultures can be found in Mammalian Cell Biotechnology: A Practical Approach, M. Butler, ed. (IRL Press, 1991) and Sambrook *et al.*, *supra*.

Methods of transfection are known to the ordinarily skilled artisan, for example, CaPO<sub>4</sub> treatment and electroporation. Depending on the host cell used, transformation is performed using standard techniques appropriate to such cells. The calcium treatment employing calcium chloride, as described in Sambrook *et al.*, *supra*, or electroporation is generally used for prokaryotes or other cells that contain substantial cell-wall barriers. Infection with *Agrobacterium tumefaciens* is used for transformation of certain plant cells, as described by Shaw *et al.*, Gene, 23: 315 (1983) and WO 89/05859 published 29 June 1989. For mammalian cells without such cell walls, the calcium phosphate precipitation method of Graham and van der Eb, Virology, 52:456-457 (1978) can be employed. General aspects of mammalian cell host system transformations have been described in U.S. Patent No. 4,399,216. Transformations into yeast are typically carried out according to the method of Van Solingen *et al.*, J. Bact., 130: 946 (1977) and Hsiao *et al.*, Proc. Natl. Acad. Sci. (USA), 76: 3829 (1979). However, other methods for introducing DNA into cells, such as by nuclear microinjection, electroporation, bacterial protoplast fusion with intact cells, or polycations, *e.g.*, polybrene or polyornithine, may also be used. For various techniques for

transforming mammalian cells, *see*, Keown *et al.*, Methods in Enzymology, **185**: 527-537 (1990) and Mansour *et al.*, Nature, **336**: 348-352 (1988).

Suitable host cells for cloning or expressing the DNA in the vectors herein include prokaryote, yeast, or higher eukaryote cells. Suitable prokaryotes include, but are not limited to, eubacteria, such as Gram-negative or Gram-positive organisms, for example, Enterobacteriaceae such as *E. coli*. Various *E. coli* strains are publicly available, such as *E. coli* K12 strain MM294 (ATCC 31,446); *E. coli* X1776 (ATCC 31,537); *E. coli* strain W3110 (ATCC 27,325); and K5 772 (ATCC 53,635). Other suitable prokaryotic host cells include Enterobacteriaceae such as *Escherichia*, *e.g.*, *E. coli*, *Enterobacter*, *Erwinia*, *Klebsiella*, *Proteus*, *Salmonella*, *e.g.*, *Salmonella typhimurium*, *Serratia*, *e.g.*, *Serratia marcescans*, and *Shigella*, as well as *Bacilli* such as *B. subtilis* and *B. licheniformis* (*e.g.*, *B. licheniformis* 41P disclosed in DD 266,710 published 12 April 1989), *Pseudomonas* such as *P. aeruginosa*, and *Streptomyces*. These examples are illustrative rather than limiting. Strain W3110 is one particularly preferred host or parent host because it is a common host strain for recombinant DNA product fermentations. Preferably, the host cell secretes minimal amounts of proteolytic enzymes. For example, strain W3110 may be modified to effect a genetic mutation in the genes encoding proteins endogenous to the host, with examples of such hosts including *E. coli* W3110 strain 1A2, which has the complete genotype *tonA*; *E. coli* W3110 strain 9E4, which has the complete genotype *tonA ptr3*; *E. coli* W3110 strain 27C7 (ATCC 55,244), which has the complete genotype *tonA ptr3 phoA E15 (argF-lac)169 degP ompT kan<sup>r</sup>*; *E. coli* W3110 strain 37D6, which has the complete genotype *tonA ptr3 phoA E15 (argF-lac)169 degP ompT rbs7 ilvG kan<sup>r</sup>*; *E. coli* W3110 strain 40B4, which is strain 37D6 with a non-kanamycin resistant *degP* deletion mutation; and an *E. coli* strain having mutant periplasmic protease disclosed in U.S. Patent No. 4,946,783 issued 7 August 1990. Alternatively, *in vitro* methods of cloning, *e.g.*, PCR or other nucleic acid polymerase reactions, are suitable.

In addition to prokaryotes, eukaryotic microbes such as filamentous fungi or yeast are suitable cloning or expression hosts for vectors encoding the PRO polypeptide. *Saccharomyces cerevisiae* is a commonly used lower eukaryotic host microorganism. Others include *Schizosaccharomyces pombe* (Beach and Nurse, Nature, **290**: 140 [1981]; EP 139,383 published 2 May 1985); *Kluyveromyces* hosts (U.S. Patent No. 4,943,529; Fleer *et al.*, Bio/Technology, **9**: 968-975 (1991)) such as, *e.g.*, *K. lactis* (MW98-8C, CBS683, CBS4574; Louvencourt *et al.*, J. Bacteriol., **737** [1983]), *K. fragilis* (ATCC 12,424), *K. bulgaricus* (ATCC 16,045), *K. wickerhamii* (ATCC 24,178), *K. waltii* (ATCC 56,500), *K. drosophilum* (ATCC 36,906; Van den Berg *et al.*, Bio/Technology, **8**: 135 (1990)), *K. thermotolerans*, and *K. marxianus*; *yarrowia* (EP 402,226); *Pichia pastoris* (EP 183,070; Sreekrishna *et al.*, J. Basic Microbiol., **28**: 265-278 [1988]); *Candida*; *Trichoderma reesia* (EP 244,234); *Neurospora crassa* (Case *et al.*, Proc. Natl. Acad. Sci. USA, **76**: 5259-5263 [1979]); *Schwanniomyces* such as *Schwanniomyces occidentalis* (EP 394,538 published 31 October 1990); and filamentous fungi such as, *e.g.*, *Neurospora*, *Penicillium*, *Tolypocladium* (WO 91/00357 published 10 January 1991), and *Aspergillus* hosts such as *A. nidulans* (Ballance *et al.*, Biochem. Biophys. Res. Commun., **112**: 284-289 [1983]; Tilburn *et al.*, Gene, **26**: 205-221 [1983]; Yelton *et al.*, Proc. Natl. Acad. Sci. USA, **81**: 1470-1474 [1984]) and *A. niger* (Kelly and Hynes, EMBO J., **4**: 475-479 [1985]). Methylophilic yeasts are suitable herein and include, but are not limited to, yeast capable of growth on methanol selected from the genera consisting of *Hansenula*, *Candida*, *Kloeckera*, *Pichia*, *Saccharomyces*,

*Torulopsis*, and *Rhodotorula*. A list of specific species that are exemplary of this class of yeasts may be found in C. Anthony, The Biochemistry of Methylophilic, 269 (1982).

Suitable host cells for the expression of nucleic acid encoding glycosylated PRO polypeptides are derived from multicellular organisms. Examples of invertebrate cells include insect cells such as *Drosophila* S2 and *Spodoptera* Sf9, as well as plant cells. Examples of useful mammalian host cell lines include Chinese hamster ovary (CHO) and COS cells. More specific examples include monkey kidney CV1 line transformed by SV40 (COS-7, ATCC CRL 1651); human embryonic kidney line (293 or 293 cells subcloned for growth in suspension culture, Graham *et al.*, J. Gen. Virol., 36: 59 (1977)); Chinese hamster ovary cells/-DHFR (CHO, Urlaub and Chasin, Proc. Natl. Acad. Sci. USA, 77:4216 (1980)); mouse sertoli cells (TM4, Mather, Biol. Reprod., 23:243-251 (1980)); human lung cells (W138, ATCC CCL 75); human liver cells (Hep G2, HB 8065); and mouse mammary tumor (MMT 060562, ATCC CCL51). The selection of the appropriate host cell is deemed to be within the skill in the art.

#### 5.2.3.3. Selection and Use of a Replicable Vector

The nucleic acid (*e.g.*, cDNA or genomic DNA) encoding the PRO polypeptide may be inserted into a replicable vector for cloning (amplification of the DNA) or for expression. Various vectors are publicly available. The vector may, for example, be in the form of a plasmid, cosmid, viral particle, or phage. The appropriate nucleic acid sequence may be inserted into the vector by a variety of procedures. In general, DNA is inserted into an appropriate restriction endonuclease site(s) using techniques known in the art. Vector components generally include, but are not limited to, one or more of a signal sequence if the sequence is to be secreted, an origin of replication, one or more marker genes, an enhancer element, a promoter, and a transcription termination sequence. Construction of suitable vectors containing one or more of these components employs standard ligation techniques that are known to the skilled artisan.

The PRO polypeptide may be produced recombinantly not only directly, but also as a fusion polypeptide with a heterologous polypeptide, which may be a signal sequence or other polypeptide having a specific cleavage site at the N-terminus of the mature protein or polypeptide. In general, the signal sequence may be a component of the vector, or it may be a part of the DNA encoding the PRO polypeptide that is inserted into the vector. The signal sequence may be a prokaryotic signal sequence selected, for example, from the group of the alkaline phosphatase, penicillinase, lpp, or heat-stable enterotoxin II leaders. For yeast secretion the signal sequence may be, *e.g.*, the yeast invertase leader, alpha factor leader (including *Saccharomyces* and *Kluyveromyces*  $\alpha$ -factor leaders, the latter described in U.S. Patent No. 5,010,182), or acid phosphatase leader, the *C. albicans* glucoamylase leader (EP 362,179 published 4 April 1990), or the signal described in WO 90/13646 published 15 November 1990. In mammalian cell expression, mammalian signal sequences may be used to direct secretion of the protein, such as signal sequences from secreted polypeptides of the same or related species, as well as viral secretory leaders.

Both expression and cloning vectors contain a nucleic acid sequence that enables the vector to replicate in one or more selected host cells. Such sequences are well known for a variety of bacteria, yeast, and viruses. The origin of replication from the plasmid pBR322 is suitable for most Gram-negative bacteria, the 2 $\mu$  plasmid origin

is suitable for yeast, and various viral origins (SV40, polyoma, adenovirus, VSV, or BPV) are useful for cloning vectors in mammalian cells.

Expression and cloning vectors will typically contain a selection gene, also termed a selectable marker. Typical selection genes encode proteins that (a) confer resistance to antibiotics or other toxins, *e.g.*, ampicillin, neomycin, methotrexate, or tetracycline, (b) complement auxotrophic deficiencies, or (c) supply critical nutrients not available from complex media, *e.g.*, the gene encoding D-alanine racemase for *Bacilli*.

An example of suitable selectable markers for mammalian cells are those that enable the identification of cells competent to take up the nucleic acid encoding the PRO polypeptide such as DHFR or thymidine kinase. An appropriate host cell when wild-type DHFR is employed is the CHO cell line deficient in DHFR activity, prepared and propagated as described by Urlaub *et al.*, Proc. Natl. Acad. Sci. USA, 77: 4216 (1980). A suitable selection gene for use in yeast is the *trp1* gene present in the yeast plasmid YRp7. Stinchcomb *et al.*, Nature, 282: 39 (1979); Kingsman *et al.*, Gene, 7: 141 (1979); Tschemper *et al.*, Gene, 10: 157 (1980). The *trp1* gene provides a selection marker for a mutant strain of yeast lacking the ability to grow in tryptophan, for example, ATCC No. 44076 or PEP4-1. Jones, Genetics, 85: 12 (1977).

Expression and cloning vectors usually contain a promoter operably linked to the nucleic acid sequence encoding the PRO polypeptide to direct mRNA synthesis. Promoters recognized by a variety of potential host cells are well known. Promoters suitable for use with prokaryotic hosts include the  $\beta$ -lactamase and lactose promoter systems (Chang *et al.*, Nature, 275: 615 (1978); Goeddel *et al.*, Nature, 281: 544 (1979)), alkaline phosphatase, a tryptophan (*trp*) promoter system (Goeddel, Nucleic Acids Res., 8: 4057 (1980); EP 36,776), and hybrid promoters such as the *tac* promoter (deBoer *et al.*, Proc. Natl. Acad. Sci. USA, 80: 21-25 (1983)). Promoters for use in bacterial systems also will contain a Shine-Dalgarno (S.D.) sequence operably linked to the DNA encoding the PRO polypeptide.

Examples of suitable promoting sequences for use with yeast hosts include the promoters for 3-phosphoglycerate kinase (Hitzeman *et al.*, J. Biol. Chem., 255: 2073 (1980)) or other glycolytic enzymes (Hess *et al.*, J. Adv. Enzyme Reg., 7: 149 (1968); Holland, Biochemistry, 17: 4900 (1978)), such as enolase, glyceraldehyde-3-phosphate dehydrogenase, hexokinase, pyruvate decarboxylase, phosphofructokinase, glucose-6-phosphate isomerase, 3-phosphoglycerate mutase, pyruvate kinase, triosephosphate isomerase, phosphoglucose isomerase, and glucokinase.

Other yeast promoters that are inducible promoters having the additional advantage of transcription controlled by growth conditions are the promoter regions for alcohol dehydrogenase 2, isocytochrome C, acid phosphatase, degradative enzymes associated with nitrogen metabolism, metallothionein, glyceraldehyde-3-phosphate dehydrogenase, and enzymes responsible for maltose and galactose utilization. Suitable vectors and promoters for use in yeast expression are further described in EP 73,657.

PRO nucleic acid transcription from vectors in mammalian host cells is controlled, for example, by promoters obtained from the genomes of viruses such as polyoma virus, fowlpox virus (UK 2,211,504 published 5 July 1989), adenovirus (such as Adenovirus 2), bovine papilloma virus, avian sarcoma virus, cytomegalovirus, a retrovirus, hepatitis-B virus, and Simian Virus 40 (SV40); by heterologous mammalian promoters, *e.g.*, the actin



promoter or an immunoglobulin promoter; and by heat-shock promoters, provided such promoters are compatible with the host cell systems.

Transcription of a DNA encoding the PRO polypeptide by higher eukaryotes may be increased by inserting an enhancer sequence into the vector. Enhancers are cis-acting elements of DNA, usually about from 10 to 300 bp, that act on a promoter to increase its transcription. Many enhancer sequences are now known from mammalian genes (globin, elastase, albumin,  $\alpha$ -fetoprotein, and insulin). Typically, however, one will use an enhancer from a eukaryotic cell virus. Examples include the SV40 enhancer on the late side of the replication origin (bp 100-270), the cytomegalovirus early promoter enhancer, the polyoma enhancer on the late side of the replication origin, and adenovirus enhancers. The enhancer may be spliced into the vector at a position 5' or 3' to the sequence coding for PRO polypeptides, but is preferably located at a site 5' from the promoter.

Expression vectors used in eukaryotic host cells (yeast, fungi, insect, plant, animal, human, or nucleated cells from other multicellular organisms) will also contain sequences necessary for the termination of transcription and for stabilizing the mRNA. Such sequences are commonly available from the 5' and, occasionally 3', untranslated regions of eukaryotic or viral DNAs or cDNAs. These regions contain nucleotide segments transcribed as polyadenylated fragments in the untranslated portion of the mRNA encoding the PRO polypeptide.

Still other methods, vectors, and host cells suitable for adaptation to the synthesis of the PRO polypeptide in recombinant vertebrate cell culture are described in Gething *et al.*, Nature, 293: 620-625 (1981); Mantei *et al.*, Nature, 281: 40-46 (1979); EP 117,060; and EP 117,058.

#### 5.2.3.4. Detecting Gene Amplification/Expression

Gene amplification and/or expression may be measured in a sample directly, for example, by conventional Southern blotting, Northern blotting to quantitate the transcription of mRNA (Thomas, Proc. Natl. Acad. Sci. USA, 77:5201-5205 (1980)), dot blotting (DNA analysis), or *in situ* hybridization, using an appropriately labeled probe, based on the sequences provided herein. Alternatively, antibodies may be employed that can recognize specific duplexes, including DNA duplexes, RNA duplexes, and DNA-RNA hybrid duplexes or DNA-protein duplexes. The antibodies in turn may be labeled and the assay may be carried out where the duplex is bound to a surface, so that upon the formation of duplex on the surface, the presence of antibody bound to the duplex can be detected.

Gene expression, alternatively, may be measured by immunological methods, such as immunohistochemical staining of cells or tissue sections and assay of cell culture or body fluids, to quantitate directly the expression of gene product. Antibodies useful for immunohistochemical staining and/or assay of sample fluids may be either monoclonal or polyclonal, and may be prepared in any mammal. Conveniently, the antibodies may be prepared against a native-sequence PRO polypeptide or against a synthetic peptide based on the DNA sequences provided herein or against exogenous sequence fused to DNA encoding the PRO polypeptide and encoding a specific antibody epitope.

#### 5.2.3.5. Purification of PRO Polypeptides

Forms of PRO polypeptides may be recovered from culture medium or from host cell lysates. If

membrane-bound, it can be released from the membrane using a suitable detergent solution (*e.g.*, TRITON-X™ 100) or by enzymatic cleavage. Cells employed in expression of nucleic acid encoding the PRO polypeptide can be disrupted by various physical or chemical means, such as freeze-thaw cycling, sonication, mechanical disruption, or cell-lysing agents. It may be desired to purify the PRO polypeptide from recombinant cell proteins or polypeptides. The following procedures are exemplary of suitable purification procedures: by fractionation on an ion-exchange column; ethanol precipitation; reverse phase HPLC; chromatography on silica or on a cation-exchange resin such as DEAE; chromatofocusing; SDS-PAGE; ammonium sulfate precipitation; gel filtration using, for example, Sephadex G-75; protein A Sepharose columns to remove contaminants such as IgG; and metal chelating columns to bind epitope-tagged forms of the PRO polypeptide. Various methods of protein purification may be employed and such methods are known in the art and described, for example, in Deutscher, Methods in Enzymology, 182 (1990); Scopes, Protein Purification: Principles and Practice (Springer-Verlag: New York, 1982). The purification step(s) selected will depend, for example, on the nature of the production process used and the particular PRO polypeptide produced.

#### 5.2.4. Uses of PRO Polypeptides

##### 5.2.4.1. Assays for Cardiovascular, Endothelial, and Angiogenic Activity

Various assays can be used to test the polypeptide herein for cardiovascular, endothelial, and angiogenic activity. Such assays include those provided in the Examples below.

Assays for testing for endothelin antagonist activity, as disclosed in U.S. Pat. No. 5,773,414, include a rat heart ventricle binding assay where the polypeptide is tested for its ability to inhibit iodinated endothelin-1 binding in a receptor assay, an endothelin receptor binding assay testing for intact cell binding of radiolabeled endothelin-1 using rabbit renal artery vascular smooth muscle cells, an inositol phosphate accumulation assay where functional activity is determined in Rat-1 cells by measuring intra-cellular levels of second messengers, an arachidonic acid release assay that measures the ability of added compounds to reduce endothelin-stimulated arachidonic acid release in cultured vascular smooth muscles, *in vitro* (isolated vessel) studies using endothelium from male New Zealand rabbits, and *in vivo* studies using male Sprague-Dawley rats.

Assays for tissue generation activity include, without limitation, those described in WO 95/16035 (bone, cartilage, tendon); WO 95/05846 (nerve, neuronal), and WO 91/07491 (skin, endothelium).

Assays for wound-healing activity include, for example, those described in Winter, Epidermal Wound Healing, Maibach, HI and Rovee, DT, eds. (Year Book Medical Publishers, Inc., Chicago), pp. 71-112, as modified by the article of Eaglstein and Mertz, J. Invest. Dermatol., 71: 382-384 (1978).

An assay to screen for a test molecule relating to a PRO polypeptide that binds an endothelin B<sub>1</sub> (ETB<sub>1</sub>) receptor polypeptide and modulates signal transduction activity involves providing a host cell transformed with a DNA encoding endothelin B<sub>1</sub> receptor polypeptide, exposing the cells to the test candidate, and measuring endothelin B<sub>1</sub> receptor signal transduction activity, as described, *e.g.*, in U.S. Pat. No. 5,773,223.

There are several cardiac hypertrophy assays. *In vitro* assays include induction of spreading of adult rat cardiac myocytes. In this assay, ventricular myocytes are isolated from a single (male Sprague-Dawley) rat,

essentially following a modification of the procedure described in detail by Piper *et al.*, "Adult ventricular rat heart muscle cells" in Cell Culture Techniques in Heart and Vessel Research, H.M. Piper, ed. (Berlin: Springer-Verlag, 1990), pp. 36-60. This procedure permits the isolation of adult ventricular myocytes and the long-term culture of these cells in the rod-shaped phenotype. Phenylephrine and Prostaglandin F<sub>2α</sub> (PGF<sub>2α</sub>) have been shown to induce a spreading response in these adult cells. The inhibition of myocyte spreading induced by PGF<sub>2α</sub> or PGF<sub>2α</sub> analogs (e.g., fluprostenol) and phenylephrine by various potential inhibitors of cardiac hypertrophy is then tested.

One example of an *in vivo* assay is a test for inhibiting cardiac hypertrophy induced by fluprostenol *in vivo*. This pharmacological model tests the ability of the PRO polypeptide to inhibit cardiac hypertrophy induced in rats (e.g., male Wistar or Sprague-Dawley) by subcutaneous injection of fluprostenol (an agonist analog of PGF<sub>2α</sub>). It is known that rats with pathologic cardiac hypertrophy induced by myocardial infarction have chronically elevated levels of extractable PGF<sub>2α</sub> in their myocardium. Lai *et al.*, Am. J. Physiol. (Heart Circ. Physiol.), 271: H2197-H2208 (1996). Accordingly, factors that can inhibit the effects of fluprostenol on myocardial growth *in vivo* are potentially useful for treating cardiac hypertrophy. The effects of the PRO polypeptide on cardiac hypertrophy are determined by measuring the weight of heart, ventricles, and left ventricle (normalized by body weight) relative to fluprostenol-treated rats not receiving the PRO polypeptide.

Another example of an *in vivo* assay is the pressure-overload cardiac hypertrophy assay. For *in vivo* testing it is common to induce pressure-overload cardiac hypertrophy by constriction of the abdominal aorta of test animals. In a typical protocol, rats (e.g., male Wistar or Sprague-Dawley) are treated under anesthesia, and the abdominal aorta of each rat is narrowed down just below the diaphragm. Beznak M., Can. J. Biochem. Physiol., 33: 985-94 (1955). The aorta is exposed through a surgical incision, and a blunted needle is placed next to the vessel. The aorta is constricted with a ligature of silk thread around the needle, which is immediately removed and which reduces the lumen of the aorta to the diameter of the needle. This approach is described, for example, in Rossi *et al.*, Am. Heart J., 124: 700-709 (1992) and O'Rourke and Reibel, P.S.E.M.B., 200: 95-100 (1992).

In yet another *in vivo* assay, the effect on cardiac hypertrophy following experimentally induced myocardial infarction (MI) is measured. Acute MI is induced in rats by left coronary artery ligation and confirmed by electrocardiographic examination. A sham-operated group of animals is also prepared as control animals. Earlier data have shown that cardiac hypertrophy is present in the group of animals with MI, as evidenced by an 18% increase in heart weight-to-body weight ratio. Lai *et al.*, *supra*. Treatment of these animals with candidate blockers of cardiac hypertrophy, e.g., the PRO polypeptide, provides valuable information about the therapeutic potential of the candidates tested. One further such assay test for induction of cardiac hypertrophy is disclosed in U.S. Pat. No. 5,773,415, using Sprague-Dawley rats.

For cancer, a variety of well-known animal models can be used to further understand the role of the genes identified herein in the development and pathogenesis of tumors, and to test the efficacy of candidate therapeutic agents, including antibodies and other antagonists of native PRO polypeptides, such as small-molecule antagonists. The *in vivo* nature of such models makes them particularly predictive of responses in human patients. Animal models of tumors and cancers (e.g., breast cancer, colon cancer, prostate cancer, lung cancer, etc.) include both non-recombinant and recombinant (transgenic) animals. Non-recombinant animal models include, for example,

rodent, *e.g.*, murine models. Such models can be generated by introducing tumor cells into syngeneic mice using standard techniques, *e.g.*, subcutaneous injection, tail vein injection, spleen implantation, intraperitoneal implantation, implantation under the renal capsule, or orthotopic implantation, *e.g.*, colon cancer cells implanted in colonic tissue. *See, e.g.*, PCT publication No. WO 97/33551, published September 18, 1997. Probably the most often used animal species in oncological studies are immunodeficient mice and, in particular, nude mice. The observation that the nude mouse with thymic hypo/aplasia could successfully act as a host for human tumor xenografts has lead to its widespread use for this purpose. The autosomal recessive *nu* gene has been introduced into a very large number of distinct congenic strains of nude mouse, including, for example, ASW, A/He, AKR, BALB/c, B10.LP, C17, C3H, C57BL, C57, CBA, DBA, DDD, I/st, NC, NFR, NFS, NFS/N, NZB, NZC, NZW, P, RIII, and SJL. In addition, a wide variety of other animals with inherited immunological defects other than the nude mouse have been bred and used as recipients of tumor xenografts. For further details *see, e.g.*, The Nude Mouse in Oncology Research, E. Boven and B. Winograd, eds. (CRC Press, Inc., 1991).

The cells introduced into such animals can be derived from known tumor/cancer cell lines, such as any of the above-listed tumor cell lines, and, for example, the B104-1-1 cell line (stable NIH-3T3 cell line transfected with the *neu* protooncogene); *ras*-transfected NIH-3T3 cells; Caco-2 (ATCC HTB-37); or a moderately well-differentiated grade II human colon adenocarcinoma cell line, HT-29 (ATCC HTB-38); or from tumors and cancers. Samples of tumor or cancer cells can be obtained from patients undergoing surgery, using standard conditions involving freezing and storing in liquid nitrogen. Karmali *et al.*, Br. J. Cancer, 48: 689-696 (1983).

Tumor cells can be introduced into animals such as nude mice by a variety of procedures. The subcutaneous (s.c.) space in mice is very suitable for tumor implantation. Tumors can be transplanted s.c. as solid blocks, as needle biopsies by use of a trochar, or as cell suspensions. For solid-block or trochar implantation, tumor tissue fragments of suitable size are introduced into the s.c. space. Cell suspensions are freshly prepared from primary tumors or stable tumor cell lines, and injected subcutaneously. Tumor cells can also be injected as subdermal implants. In this location, the inoculum is deposited between the lower part of the dermal connective tissue and the s.c. tissue.

Animal models of breast cancer can be generated, for example, by implanting rat neuroblastoma cells (from which the *neu* oncogene was initially isolated), or *neu*-transformed NIH-3T3 cells into nude mice, essentially as described by Drebin *et al.* Proc. Nat. Acad. Sci. USA, 83: 9129-9133 (1986).

Similarly, animal models of colon cancer can be generated by passaging colon cancer cells in animals, *e.g.*, nude mice, leading to the appearance of tumors in these animals. An orthotopic transplant model of human colon cancer in nude mice has been described, for example, by Wang *et al.*, Cancer Research, 54: 4726-4728 (1994) and Too *et al.*, Cancer Research, 55: 681-684 (1995). This model is based on the so-called "METAMOUSE™" sold by AntiCancer, Inc., (San Diego, California).

Tumors that arise in animals can be removed and cultured *in vitro*. Cells from the *in vitro* cultures can then be passaged to animals. Such tumors can serve as targets for further testing or drug screening. Alternatively, the tumors resulting from the passage can be isolated and RNA from pre-passage cells and cells isolated after one or more rounds of passage analyzed for differential expression of genes of interest. Such passaging techniques can

be performed with any known tumor or cancer cell lines.

For example, Meth A, CMS4, CMS5, CMS21, and WEHI-164 are chemically induced fibrosarcomas of BALB/c female mice (DeLeo *et al.*, J. Exp. Med., **146**: 720 (1977)), which provide a highly controllable model system for studying the anti-tumor activities of various agents. Palladino *et al.*, J. Immunol., **138**: 4023-4032 (1987). Briefly, tumor cells are propagated *in vitro* in cell culture. Prior to injection into the animals, the cell lines are washed and suspended in buffer, at a cell density of about  $10 \times 10^6$  to  $10 \times 10^7$  cells/ml. The animals are then infected subcutaneously with 10 to 100  $\mu$ l of the cell suspension, allowing one to three weeks for a tumor to appear.

In addition, the Lewis lung (3LL) carcinoma of mice, which is one of the most thoroughly studied experimental tumors, can be used as an investigational tumor model. Efficacy in this tumor model has been correlated with beneficial effects in the treatment of human patients diagnosed with small-cell carcinoma of the lung (SCCL). This tumor can be introduced in normal mice upon injection of tumor fragments from an affected mouse or of cells maintained in culture. Zupi *et al.*, Br. J. Cancer, **41**: suppl. 4, 30 (1980). Evidence indicates that tumors can be started from injection of even a single cell and that a very high proportion of infected tumor cells survive. For further information about this tumor model see, Zacharski, Haemostasis, **16**: 300-320 (1986).

One way of evaluating the efficacy of a test compound in an animal model with an implanted tumor is to measure the size of the tumor before and after treatment. Traditionally, the size of implanted tumors has been measured with a slide caliper in two or three dimensions. The measure limited to two dimensions does not accurately reflect the size of the tumor; therefore, it is usually converted into the corresponding volume by using a mathematical formula. However, the measurement of tumor size is very inaccurate. The therapeutic effects of a drug candidate can be better described as treatment-induced growth delay and specific growth delay. Another important variable in the description of tumor growth is the tumor volume doubling time. Computer programs for the calculation and description of tumor growth are also available, such as the program reported by Rygaard and Spang-Thomsen, Proc. 6th Int. Workshop on Immune-Deficient Animals, Wu and Sheng eds. (Basel, 1989), p. 301. It is noted, however, that necrosis and inflammatory responses following treatment may actually result in an increase in tumor size, at least initially. Therefore, these changes need to be carefully monitored, by a combination of a morphometric method and flow cytometric analysis.

Further, recombinant (transgenic) animal models can be engineered by introducing the coding portion of the PRO gene identified herein into the genome of animals of interest, using standard techniques for producing transgenic animals. Animals that can serve as a target for transgenic manipulation include, without limitation, mice, rats, rabbits, guinea pigs, sheep, goats, pigs, and non-human primates, *e.g.*, baboons, chimpanzees and monkeys. Techniques known in the art to introduce a transgene into such animals include pronucleic microinjection (U.S. Patent No. 4,873,191); retrovirus-mediated gene transfer into germ lines (*e.g.*, Van der Putten *et al.*, Proc. Natl. Acad. Sci. USA, **82**: 6148-615 (1985)); gene targeting in embryonic stem cells (Thompson *et al.*, Cell, **56**: 313-321 (1989)); electroporation of embryos (Lo, Mol. Cell. Biol., **3**: 1803-1814 (1983)); and sperm-mediated gene transfer. Lavitrano *et al.*, Cell, **57**: 717-73 (1989). For a review, see for example, U.S. Patent No. 4,736,866.

For the purpose of the present invention, transgenic animals include those that carry the transgene only in part of their cells ("mosaic animals"). The transgene can be integrated either as a single transgene, or in

concatamers, e.g., head-to-head or head-to-tail tandems. Selective introduction of a transgene into a particular cell type is also possible by following, for example, the technique of Lasko *et al.*, Proc. Natl. Acad. Sci. USA, **89**: 6232-636 (1992). The expression of the transgene in transgenic animals can be monitored by standard techniques. For example, Southern blot analysis or PCR amplification can be used to verify the integration of the transgene. The level of mRNA expression can then be analyzed using techniques such as *in situ* hybridization, Northern blot analysis, PCR, or immunocytochemistry. The animals are further examined for signs of tumor or cancer development.

Alternatively, "knock-out" animals can be constructed that have a defective or altered gene encoding a PRO polypeptide identified herein, as a result of homologous recombination between the endogenous gene encoding the PRO polypeptide and altered genomic DNA encoding the same polypeptide introduced into an embryonic cell of the animal. For example, cDNA encoding a particular PRO polypeptide can be used to clone genomic DNA encoding that polypeptide in accordance with established techniques. A portion of the genomic DNA encoding a particular PRO polypeptide can be deleted or replaced with another gene, such as a gene encoding a selectable marker that can be used to monitor integration. Typically, several kilobases of unaltered flanking DNA (both at the 5' and 3' ends) are included in the vector. See, e.g., Thomas and Capecchi, Cell, **51**: 503 (1987) for a description of homologous recombination vectors. The vector is introduced into an embryonic stem cell line (e.g., by electroporation) and cells in which the introduced DNA has homologously recombined with the endogenous DNA are selected. See, e.g., Li *et al.*, Cell, **69**: 915 (1992). The selected cells are then injected into a blastocyst of an animal (e.g., a mouse or rat) to form aggregation chimeras. See, e.g., Bradley, in Teratocarcinomas and Embryonic Stem Cells: A Practical Approach, E. J. Robertson, ed. (IRL: Oxford, 1987), pp. 113-152. A chimeric embryo can then be implanted into a suitable pseudopregnant female foster animal and the embryo brought to term to create a "knock-out" animal. Progeny harboring the homologously recombined DNA in their germ cells can be identified by standard techniques and used to breed animals in which all cells of the animal contain the homologously recombined DNA. Knockout animals can be characterized, for instance, by their ability to defend against certain pathological conditions and by their development of pathological conditions due to absence of the PRO polypeptide.

The efficacy of antibodies specifically binding the PRO polypeptides identified herein, and other drug candidates, can be tested also in the treatment of spontaneous animal tumors. A suitable target for such studies is the feline oral squamous cell carcinoma (SCC). Feline oral SCC is a highly invasive, malignant tumor that is the most common oral malignancy of cats, accounting for over 60% of the oral tumors reported in this species. It rarely metastasizes to distant sites, although this low incidence of metastasis may merely be a reflection of the short survival times for cats with this tumor. These tumors are usually not amenable to surgery, primarily because of the anatomy of the feline oral cavity. At present, there is no effective treatment for this tumor. Prior to entry into the study, each cat undergoes complete clinical examination and biopsy, and is scanned by computed tomography (CT). Cats diagnosed with sublingual oral squamous cell tumors are excluded from the study. The tongue can become paralyzed as a result of such tumor, and even if the treatment kills the tumor, the animals may not be able to feed themselves. Each cat is treated repeatedly, over a longer period of time. Photographs of the tumors will be taken daily during the treatment period, and at each subsequent recheck. After treatment, each cat undergoes another CT

scan. CT scans and thoracic radiograms are evaluated every 8 weeks thereafter. The data are evaluated for differences in survival, response, and toxicity as compared to control groups. Positive response may require evidence of tumor regression, preferably with improvement of quality of life and/or increased life span.

In addition, other spontaneous animal tumors, such as fibrosarcoma, adenocarcinoma, lymphoma, chondroma, or leiomyosarcoma of dogs, cats, and baboons can also be tested. Of these, mammary adenocarcinoma in dogs and cats is a preferred model as its appearance and behavior are very similar to those in humans. However, the use of this model is limited by the rare occurrence of this type of tumor in animals.

Other *in vitro* and *in vivo* cardiovascular, endothelial, and angiogenic tests known in the art are also suitable herein.

#### 5.2.4.2. Tissue Distribution

The results of the cardiovascular, endothelial, and angiogenic assays herein can be verified by further studies, such as by determining mRNA expression in various human tissues.

As noted before, gene amplification and/or gene expression in various tissues may be measured by conventional Southern blotting, Northern blotting to quantitate the transcription of mRNA (Thomas, Proc. Natl. Acad. Sci. USA, 77:5201-5205 (1980)), dot blotting (DNA analysis), or *in situ* hybridization, using an appropriately labeled probe, based on the sequences provided herein. Alternatively, antibodies may be employed that can recognize specific duplexes, including DNA duplexes, RNA duplexes, and DNA-RNA hybrid duplexes or DNA-protein duplexes.

Gene expression in various tissues, alternatively, may be measured by immunological methods, such as immunohistochemical staining of tissue sections and assay of cell culture or body fluids, to quantitate directly the expression of gene product. Antibodies useful for immunohistochemical staining and/or assay of sample fluids may be either monoclonal or polyclonal, and may be prepared in any mammal. Conveniently, the antibodies may be prepared against a native-sequence PRO polypeptide or against a synthetic peptide based on the DNA sequences provided herein or against exogenous sequence fused to PRO DNA and encoding a specific antibody epitope. General techniques for generating antibodies, and special protocols for *in situ* hybridization are provided hereinbelow.

#### 5.2.4.3. Antibody Binding Studies

The results of the cardiovascular, endothelial, and angiogenic study can be further verified by antibody binding studies, in which the ability of anti-PRO antibodies to inhibit the effect of the PRO polypeptides on endothelial cells or other cells used in the cardiovascular, endothelial, and angiogenic assays is tested. Exemplary antibodies include polyclonal, monoclonal, humanized, bispecific, and heteroconjugate antibodies, the preparation of which will be described hereinbelow.

Antibody binding studies may be carried out in any known assay method, such as competitive binding assays, direct and indirect sandwich assays, and immunoprecipitation assays. Zola, Monoclonal Antibodies: A Manual of Techniques (CRC Press, Inc., 1987), pp.147-158.

Competitive binding assays rely on the ability of a labeled standard to compete with the test sample analyte for binding with a limited amount of antibody. The amount of target protein in the test sample is inversely proportional to the amount of standard that becomes bound to the antibodies. To facilitate determining the amount of standard that becomes bound, the antibodies preferably are insolubilized before or after the competition, so that the standard and analyte that are bound to the antibodies may conveniently be separated from the standard and analyte that remain unbound.

Sandwich assays involve the use of two antibodies, each capable of binding to a different immunogenic portion, or epitope, of the protein to be detected. In a sandwich assay, the test sample analyte is bound by a first antibody that is immobilized on a solid support, and thereafter a second antibody binds to the analyte, thus forming an insoluble three-part complex. *See, e.g.*, U.S. Pat. No. 4,376,110. The second antibody may itself be labeled with a detectable moiety (direct sandwich assays) or may be measured using an anti-immunoglobulin antibody that is labeled with a detectable moiety (indirect sandwich assay). For example, one type of sandwich assay is an ELISA assay, in which case the detectable moiety is an enzyme.

For immunohistochemistry, the tissue sample may be fresh or frozen or may be embedded in paraffin and fixed with a preservative such as formalin, for example.

#### 5.2.4.4. Cell-Based Tumor Assays

Cell-based assays and animal models for cardiovascular, endothelial, and angiogenic disorders, such as tumors, can be used to verify the findings of a cardiovascular, endothelial, and angiogenic assay herein, and further to understand the relationship between the genes identified herein and the development and pathogenesis of undesirable cardiovascular, endothelial, and angiogenic cell growth. The role of gene products identified herein in the development and pathology of undesirable cardiovascular, endothelial, and angiogenic cell growth, *e.g.*, tumor cells, can be tested by using cells or cells lines that have been identified as being stimulated or inhibited by the PRO polypeptide herein. Such cells include, for example, those set forth in the Examples below.

In a different approach, cells of a cell type known to be involved in a particular cardiovascular, endothelial, and angiogenic disorder are transfected with the cDNAs herein, and the ability of these cDNAs to induce excessive growth or inhibit growth is analyzed. If the cardiovascular, endothelial, and angiogenic disorder is cancer, suitable tumor cells include, for example, stable tumor cell lines such as the B104-1-1 cell line (stable NIH-3T3 cell line transfected with the *neu* protooncogene) and *ras*-transfected NIH-3T3 cells, which can be transfected with the desired gene and monitored for tumorigenic growth. Such transfected cell lines can then be used to test the ability of poly- or monoclonal antibodies or antibody compositions to inhibit tumorigenic cell growth by exerting cytostatic or cytotoxic activity on the growth of the transformed cells, or by mediating antibody-dependent cellular cytotoxicity (ADCC). Cells transfected with the coding sequences of the genes identified herein can further be used to identify drug candidates for the treatment of cardiovascular, endothelial, and angiogenic disorders such as cancer.

In addition, primary cultures derived from tumors in transgenic animals (as described above) can be used in the cell-based assays herein, although stable cell lines are preferred. Techniques to derive continuous cell lines from transgenic animals are well known in the art. *See, e.g.*, Small *et al.*, Mol. Cell. Biol., 5: 642-648 (1985).



#### 5.2.4.5. Gene Therapy

Described below are methods and compositions whereby disease symptoms may be ameliorated. Certain diseases are brought about, at least in part, by an excessive level of gene product, or by the presence of a gene product exhibiting an abnormal or excessive activity. As such, the reduction in the level and/or activity of such gene products would bring about the amelioration of such disease symptoms.

Alternatively, certain other diseases are brought about, at least in part, by the absence or reduction of the level of gene expression, or a reduction in the level of a gene product's activity. As such, an increase in the level of gene expression and/or the activity of such gene products would bring about the amelioration of such disease symptoms.

In some cases, the up-regulation of a gene in a disease state reflects a protective role for that gene product in responding to the disease condition. Enhancement of such a target gene's expression, or the activity of the target gene product, will reinforce the protective effect it exerts. Some disease states may result from an abnormally low level of activity of such a protective gene. In these cases also, an increase in the level of gene expression and/or the activity of such gene products would bring about the amelioration of such disease symptoms.

The PRO polypeptides described herein and polypeptidyl agonists and antagonists may be employed in accordance with the present invention by expression of such polypeptides *in vivo*, which is often referred to as gene therapy.

There are two major approaches to getting the nucleic acid (optionally contained in a vector) into the patient's cells: *in vivo* and *ex vivo*. For *in vivo* delivery the nucleic acid is injected directly into the patient, usually at the sites where the PRO polypeptide is required, *i.e.*, the site of synthesis of the PRO polypeptide, if known, and the site (*e.g.*, wound) where biological activity of the PRO polypeptide is needed. For *ex vivo* treatment, the patient's cells are removed, the nucleic acid is introduced into these isolated cells, and the modified cells are administered to the patient either directly or, for example, encapsulated within porous membranes that are implanted into the patient (*see, e.g.*, U.S. Pat. Nos. 4,892,538 and 5,283,187). There are a variety of techniques available for introducing nucleic acids into viable cells. The techniques vary depending upon whether the nucleic acid is transferred into cultured cells *in vitro*, or transferred *in vivo* in the cells of the intended host. Techniques suitable for the transfer of nucleic acid into mammalian cells *in vitro* include the use of liposomes, electroporation, microinjection, transduction, cell fusion, DEAE-dextran, the calcium phosphate precipitation method, etc. Transduction involves the association of a replication-defective, recombinant viral (preferably retroviral) particle with a cellular receptor, followed by introduction of the nucleic acids contained by the particle into the cell. A commonly used vector for *ex vivo* delivery of the gene is a retrovirus.

The currently preferred *in vivo* nucleic acid transfer techniques include transfection with viral or non-viral vectors (such as adenovirus, lentivirus, Herpes simplex I virus, or adeno-associated virus (AAV)) and lipid-based systems (useful lipids for lipid-mediated transfer of the gene are, for example, DOTMA, DOPE, and DC-Chol; *see, e.g.*, Tonkinson *et al.*, Cancer Investigation, 14(1): 54-65 (1996)). The most preferred vectors for use in gene therapy are viruses, most preferably adenoviruses, AAV, lentiviruses, or retroviruses. A viral vector such as a retroviral vector includes at least one transcriptional promoter/enhancer or locus-defining element(s), or other

elements that control gene expression by other means such as alternate splicing, nuclear RNA export, or post-translational modification of messenger. In addition, a viral vector such as a retroviral vector includes a nucleic acid molecule that, when transcribed in the presence of a gene encoding the PRO polypeptide, is operably linked thereto and acts as a translation initiation sequence. Such vector constructs also include a packaging signal, long terminal repeats (LTRs) or portions thereof, and positive and negative strand primer binding sites appropriate to the virus used (if these are not already present in the viral vector). In addition, such vector typically includes a signal sequence for secretion of the PRO polypeptide from a host cell in which it is placed. Preferably the signal sequence for this purpose is a mammalian signal sequence, most preferably the native signal sequence for the PRO polypeptide. Optionally, the vector construct may also include a signal that directs polyadenylation, as well as one or more restriction sites and a translation termination sequence. By way of example, such vectors will typically include a 5' LTR, a tRNA binding site, a packaging signal, an origin of second-strand DNA synthesis, and a 3' LTR or a portion thereof. Other vectors can be used that are non-viral, such as cationic lipids, polylysine, and dendrimers.

In some situations, it is desirable to provide the nucleic acid source with an agent that targets the target cells, such as an antibody specific for a cell-surface membrane protein or the target cell, a ligand for a receptor on the target cell, etc. Where liposomes are employed, proteins that bind to a cell-surface membrane protein associated with endocytosis may be used for targeting and/or to facilitate uptake; *e.g.*, capsid proteins or fragments thereof tropic for a particular cell type, antibodies for proteins that undergo internalization in cycling, and proteins that target intracellular localization and enhance intracellular half-life. The technique of receptor-mediated endocytosis is described, for example, by Wu *et al.*, J. Biol. Chem., **262**: 4429-4432 (1987); and Wagner *et al.*, Proc. Natl. Acad. Sci. USA, **87**: 3410-3414 (1990). For a review of the currently known gene marking and gene therapy protocols, see, Anderson *et al.*, Science, **256**: 808-813 (1992). See also WO 93/25673 and the references cited therein.

Suitable gene therapy and methods for making retroviral particles and structural proteins can be found in, *e.g.*, U.S. Pat. No. 5,681,746.

#### 5.2.4.6. Use of Gene as a Diagnostic

This invention is also related to the use of the gene encoding the PRO polypeptide as a diagnostic. Detection of a mutated form of the PRO polypeptide will allow a diagnosis of a cardiovascular, endothelial, and angiogenic disease or a susceptibility to a cardiovascular, endothelial, and angiogenic disease, such as a tumor, since mutations in the PRO polypeptide may cause tumors.

Individuals carrying mutations in the genes encoding a human PRO polypeptide may be detected at the DNA level by a variety of techniques. Nucleic acids for diagnosis may be obtained from a patient's cells, such as from blood, urine, saliva, tissue biopsy, and autopsy material. The genomic DNA may be used directly for detection or may be amplified enzymatically by using PCR (Saiki *et al.*, Nature, **324**: 163-166 (1986)) prior to analysis. RNA or cDNA may also be used for the same purpose. As an example, PCR primers complementary to the nucleic acid encoding the PRO polypeptide can be used to identify and analyze the PRO polypeptide mutations. For example, deletions and insertions can be detected by a change in size of the amplified product in comparison to the normal

genotype. Point mutations can be identified by hybridizing amplified DNA to radiolabeled RNA encoding the PRO polypeptide, or alternatively, radiolabeled antisense DNA sequences encoding the PRO polypeptide. Perfectly matched sequences can be distinguished from mismatched duplexes by RNase A digestion or by differences in melting temperatures.

5 Genetic testing based on DNA sequence differences may be achieved by detection of alteration in electrophoretic mobility of DNA fragments in gels with or without denaturing agents. Small sequence deletions and insertions can be visualized by high resolution gel electrophoresis. DNA fragments of different sequences may be distinguished on denaturing formamide gradient gels in which the mobilities of different DNA fragments are retarded in the gel at different positions according to their specific melting or partial melting temperatures. *See, e.g., Myers et al., Science, 230: 1242 (1985).*

10 Sequence changes at specific locations may also be revealed by nuclease protection assays, such as RNase and S1 protection or the chemical cleavage method, for example, Cotton *et al.*, Proc. Natl. Acad. Sci. USA, **85**: 4397-4401 (1985).

15 Thus, the detection of a specific DNA sequence may be achieved by methods such as hybridization, RNase protection, chemical cleavage, direct DNA sequencing, or the use of restriction enzymes, *e.g.*, restriction fragment length polymorphisms (RFLP), and Southern blotting of genomic DNA.

#### 5.2.4.7. Use to Detect PRO Polypeptide Levels

In addition to more conventional gel-electrophoresis and DNA sequencing, mutations can also be detected by *in situ* analysis.

20 Expression of nucleic acid encoding the PRO polypeptide may be linked to vascular disease or neovascularization associated with tumor formation. If the PRO polypeptide has a signal sequence and the mRNA is highly expressed in endothelial cells and to a lesser extent in smooth muscle cells, this indicates that the PRO polypeptide is present in serum. Accordingly, an anti-PRO polypeptide antibody could be used to diagnose vascular disease or neovascularization associated with tumor formation, since an altered level of this PRO polypeptide may be indicative of such disorders.

25 A competition assay may be employed wherein antibodies specific to the PRO polypeptide are attached to a solid support and the labeled PRO polypeptide and a sample derived from the host are passed over the solid support and the amount of label detected attached to the solid support can be correlated to a quantity of the PRO polypeptide in the sample.

#### 30 5.2.4.8. Chromosome Mapping

The sequences of the present invention are also valuable for chromosome identification. The sequence is specifically targeted to and can hybridize with a particular location on an individual human chromosome. Moreover, there is a current need for identifying particular sites on the chromosome. Few chromosome marking reagents based on actual sequence data (repeat polymorphisms) are presently available for marking chromosomal location. The mapping of DNAs to chromosomes according to the present invention is an important first step in

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correlating those sequences with genes associated with disease.

Briefly, sequences can be mapped to chromosomes by preparing PCR primers (preferably 15-25 bp) from the cDNA. Computer analysis for the 3'- untranslated region is used to rapidly select primers that do not span more than one exon in the genomic DNA, thus complicating the amplification process. These primers are then used for PCR screening of somatic cell hybrids containing individual human chromosomes. Only those hybrids containing the human gene corresponding to the primer will yield an amplified fragment.

PCR mapping of somatic cell hybrids is a rapid procedure for assigning a particular DNA to a particular chromosome. Using the present invention with the same oligonucleotide primers, sublocalization can be achieved with panels of fragments from specific chromosomes or pools of large genomic clones in an analogous manner. Other mapping strategies that can similarly be used to map to its chromosome include *in situ* hybridization, prescreening with labeled flow-sorted chromosomes, and preselection by hybridization to construct chromosome-specific cDNA libraries.

Fluorescence *in situ* hybridization (FISH) of a cDNA clone to a metaphase chromosomal spread can be used to provide a precise chromosomal location in one step. This technique can be used with cDNA as short as 500 or 600 bases; however, clones larger than 2,000 bp have a higher likelihood of binding to a unique chromosomal location with sufficient signal intensity for simple detection. FISH requires use of the clones from which the gene encoding the PRO polypeptide was derived, and the longer the better. For example, 2,000 bp is good, 4,000 bp is better, and more than 4,000 is probably not necessary to get good results a reasonable percentage of the time. For a review of this technique, see, Verma *et al.*, Human Chromosomes: a Manual of Basic Techniques (Pergamon Press, New York, 1988).

Once a sequence has been mapped to a precise chromosomal location, the physical position of the sequence on the chromosome can be correlated with genetic map data. Such data are found, for example, in V. McKusick, Mendelian Inheritance in Man (available online through Johns Hopkins University Welch Medical Library). The relationship between genes and diseases that have been mapped to the same chromosomal region is then identified through linkage analysis (coinheritance of physically adjacent genes).

Next, it is necessary to determine the differences in the cDNA or genomic sequence between affected and unaffected individuals. If a mutation is observed in some or all of the affected individuals but not in any normal individuals, then the mutation is likely to be the causative agent of the disease.

With current resolution of physical mapping and genetic mapping techniques, a cDNA precisely localized to a chromosomal region associated with the disease could be one of between 50 and 500 potential causative genes. (This assumes 1 megabase mapping resolution and one gene per 20 kb).

#### 5.2.4.9. Screening Assays for Drug Candidates

This invention encompasses methods of screening compounds to identify those that mimic the PRO polypeptide (agonists) or prevent the effect of the PRO polypeptide (antagonists). Screening assays for antagonist drug candidates are designed to identify compounds that bind or complex with the PRO polypeptide encoded by the genes identified herein, or otherwise interfere with the interaction of the encoded polypeptides with other

cellular proteins. Such screening assays will include assays amenable to high-throughput screening of chemical libraries, making them particularly suitable for identifying small molecule drug candidates.

The assays can be performed in a variety of formats, including protein-protein binding assays, biochemical screening assays, immunoassays, and cell-based assays, which are well characterized in the art.

5 All assays for antagonists are common in that they call for contacting the drug candidate with a PRO polypeptide encoded by a nucleic acid identified herein under conditions and for a time sufficient to allow these two components to interact.

10 In binding assays, the interaction is binding and the complex formed can be isolated or detected in the reaction mixture. In a particular embodiment, the PRO polypeptide encoded by the gene identified herein or the drug candidate is immobilized on a solid phase, *e.g.*, on a microtiter plate, by covalent or non-covalent attachments. Non-covalent attachment generally is accomplished by coating the solid surface with a solution of the PRO polypeptide and drying. Alternatively, an immobilized antibody, *e.g.*, a monoclonal antibody, specific for the PRO polypeptide to be immobilized can be used to anchor it to a solid surface. The assay is performed by adding the non-immobilized component, which may be labeled by a detectable label, to the immobilized component, *e.g.*, the  
15 coated surface containing the anchored component. When the reaction is complete, the non-reacted components are removed, *e.g.*, by washing, and complexes anchored on the solid surface are detected. When the originally non-immobilized component carries a detectable label, the detection of label immobilized on the surface indicates that complexing occurred. Where the originally non-immobilized component does not carry a label, complexing can be detected, for example, by using a labeled antibody specifically binding the immobilized complex.

20 If the candidate compound interacts with but does not bind to a particular PRO polypeptide encoded by a gene identified herein, its interaction with that polypeptide can be assayed by methods well known for detecting protein-protein interactions. Such assays include traditional approaches, such as, *e.g.*, cross-linking, co-immunoprecipitation, and co-purification through gradients or chromatographic columns. In addition, protein-protein interactions can be monitored by using a yeast-based genetic system described by Fields and co-workers (Fields and Song, Nature (London), 340: 245-246 (1989); Chien *et al.*, Proc. Natl. Acad. Sci. USA, 88: 9578-9582  
25 (1991)) as disclosed by Chevray and Nathans, Proc. Natl. Acad. Sci. USA, 89: 5789-5793 (1991). Many transcriptional activators, such as yeast GAL4, consist of two physically discrete modular domains, one acting as the DNA-binding domain, the other one functioning as the transcription-activation domain. The yeast expression system described in the foregoing publications (generally referred to as the "two-hybrid system") takes advantage  
30 of this property, and employs two hybrid proteins, one in which the target protein is fused to the DNA-binding domain of GAL4, and another, in which candidate activating proteins are fused to the activation domain. The expression of a GAL1-*lacZ* reporter gene under control of a GAL4-activated promoter depends on reconstitution of GAL4 activity via protein-protein interaction. Colonies containing interacting polypeptides are detected with a chromogenic substrate for  $\beta$ -galactosidase. A complete kit (MATCHMAKER™) for identifying protein-protein  
35 interactions between two specific proteins using the two-hybrid technique is commercially available from Clontech. This system can also be extended to map protein domains involved in specific protein interactions as well as to pinpoint amino acid residues that are crucial for these interactions.

Compounds that interfere with the interaction of a gene encoding a PRO polypeptide identified herein and other intra- or extracellular components can be tested as follows: usually a reaction mixture is prepared containing the product of the gene and the intra- or extracellular component under conditions and for a time allowing for the interaction and binding of the two products. To test the ability of a candidate compound to inhibit binding, the reaction is run in the absence and in the presence of the test compound. In addition, a placebo may be added to a third reaction mixture, to serve as positive control. The binding (complex formation) between the test compound and the intra- or extracellular component present in the mixture is monitored as described hereinabove. The formation of a complex in the control reaction(s) but not in the reaction mixture containing the test compound indicates that the test compound interferes with the interaction of the test compound and its reaction partner.

If the PRO polypeptide has the ability to stimulate the proliferation of endothelial cells in the presence of the co-mitogen ConA, then one example of a screening method takes advantage of this ability. Specifically, in the proliferation assay, human umbilical vein endothelial cells are obtained and cultured in 96-well flat-bottomed culture plates (Costar, Cambridge, MA) and supplemented with a reaction mixture appropriate for facilitating proliferation of the cells, the mixture containing Con-A (Calbiochem, La Jolla, CA). Con-A and the compound to be screened are added and after incubation at 37°C, cultures are pulsed with <sup>3</sup>H-thymidine and harvested onto glass fiber filters (phD; Cambridge Technology, Watertown, MA). Mean <sup>3</sup>H- thymidine incorporation (cpm) of triplicate cultures is determined using a liquid scintillation counter (Beckman Instruments, Irvine, CA). Significant <sup>3</sup>(H)-thymidine incorporation indicates stimulation of endothelial cell proliferation.

To assay for antagonists, the assay described above is performed; however, in this assay the PRO polypeptide is added along with the compound to be screened and the ability of the compound to inhibit <sup>3</sup>(H)thymidine incorporation in the presence of the PRO polypeptide indicates that the compound is an antagonist to the PRO polypeptide. Alternatively, antagonists may be detected by combining the PRO polypeptide and a potential antagonist with membrane-bound PRO polypeptide receptors or recombinant receptors under appropriate conditions for a competitive inhibition assay. The PRO polypeptide can be labeled, such as by radioactivity, such that the number of PRO polypeptide molecules bound to the receptor can be used to determine the effectiveness of the potential antagonist. The gene encoding the receptor can be identified by numerous methods known to those of skill in the art, for example, ligand panning and FACS sorting. Coligan *et al.*, Current Protocols in Immun., 1(2): Chapter 5 (1991). Preferably, expression cloning is employed wherein polyadenylated RNA is prepared from a cell responsive to the PRO polypeptide and a cDNA library created from this RNA is divided into pools and used to transfect COS cells or other cells that are not responsive to the PRO polypeptide. Transfected cells that are grown on glass slides are exposed to the labeled PRO polypeptide. The PRO polypeptide can be labeled by a variety of means including iodination or inclusion of a recognition site for a site-specific protein kinase. Following fixation and incubation, the slides are subjected to autoradiographic analysis. Positive pools are identified and sub-pools are prepared and re-transfected using an interactive sub-pooling and re-screening process, eventually yielding a single clone that encodes the putative receptor.

As an alternative approach for receptor identification, the labeled PRO polypeptide can be photoaffinity-linked with cell membrane or extract preparations that express the receptor molecule. Cross-linked material is

resolved by PAGE and exposed to X-ray film. The labeled complex containing the receptor can be excised, resolved into peptide fragments, and subjected to protein micro-sequencing. The amino acid sequence obtained from micro-sequencing would be used to design a set of degenerate oligonucleotide probes to screen a cDNA library to identify the gene encoding the putative receptor.

5 In another assay for antagonists, mammalian cells or a membrane preparation expressing the receptor would be incubated with the labeled PRO polypeptide in the presence of the candidate compound. The ability of the compound to enhance or block this interaction could then be measured.

The compositions useful in the treatment of cardiovascular, endothelial, and angiogenic disorders include, without limitation, antibodies, small organic and inorganic molecules, peptides, phosphopeptides, antisense and  
10 ribozyme molecules, triple-helix molecules, etc., that inhibit the expression and/or activity of the target gene product.

More specific examples of potential antagonists include an oligonucleotide that binds to the fusions of immunoglobulin with a PRO polypeptide, and, in particular, antibodies including, without limitation, poly- and monoclonal antibodies and antibody fragments, single-chain antibodies, anti-idiotypic antibodies, and chimeric or  
15 humanized versions of such antibodies or fragments, as well as human antibodies and antibody fragments. Alternatively, a potential antagonist may be a closely related protein, for example, a mutated form of the PRO polypeptide that recognizes the receptor but imparts no effect, thereby competitively inhibiting the action of the PRO polypeptide.

Another potential PRO polypeptide antagonist is an antisense RNA or DNA construct prepared using  
20 antisense technology, where, *e.g.*, an antisense RNA or DNA molecule acts to block directly the translation of mRNA by hybridizing to targeted mRNA and preventing protein translation. Antisense technology can be used to control gene expression through triple-helix formation or antisense DNA or RNA, both of which methods are based on binding of a polynucleotide to DNA or RNA. For example, the 5' coding portion of the polynucleotide sequence, which encodes the mature PRO polypeptides herein, is used to design an antisense RNA oligonucleotide  
25 of from about 10 to 40 base pairs in length. A DNA oligonucleotide is designed to be complementary to a region of the gene involved in transcription (triple helix - *see*, Lee *et al.*, Nucl. Acids Res., **6**:3073 (1979); Cooney *et al.*, Science, **241**: 456 (1988); Dervan *et al.*, Science, **251**:1360 (1991)), thereby preventing transcription and the production of the PRO polypeptide. A sequence "complementary" to a portion of an RNA, as referred to herein, means a sequence having sufficient complementarity to be able to hybridize with the RNA, forming a stable duplex;  
30 in the case of double-stranded antisense nucleic acids, a single strand of the duplex DNA may thus be tested, or triplex helix formation may be assayed. The ability to hybridize will depend on both the degree of complementarity and the length of the antisense nucleic acid. Generally, the longer the hybridizing nucleic acid, the more base mismatches with an RNA it may contain and still form a stable duplex (or triplex, as the case may be). One skilled in the art can ascertain a tolerable degree of mismatch by use of standard procedures to determine the melting point  
35 of the hybridized complex. The antisense RNA oligonucleotide hybridizes to the mRNA *in vivo* and blocks translation of the mRNA molecule into the PRO polypeptide (antisense - Okano, Neurochem., **56**:560 (1991); Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression (CRC Press: Boca Raton, FL, 1988).

The antisense oligonucleotides can be DNA or RNA or chimeric mixtures or derivatives or modified versions thereof, single-stranded or double-stranded. The oligonucleotide can be modified at the base moiety, sugar moiety, or phosphate backbone, for example, to improve stability of the molecule, hybridization, etc. The oligonucleotide may include other appended groups such as peptides (e.g., for targeting host cell receptors *in vivo*), or agents facilitating transport across the cell membrane (see, e.g., Letsinger, *et al.*, 1989, *Proc. Natl. Acad. Sci. U.S.A.* 86:6553-6556; Lemaitre, *et al.*, 1987, *Proc. Natl. Acad. Sci. U.S.A.* 84:648-652; PCT Publication No. WO88/09810, published December 15, 1988) or the blood-brain barrier (see, e.g., PCT Publication No. WO89/10134, published April 25, 1988), hybridization-triggered cleavage agents (see, e.g., Krol *et al.*, 1988, *BioTechniques* 6:958-976) or intercalating agents (see, e.g., Zon, 1988, *Pharm. Res.* 5:539-549). To this end, the oligonucleotide may be conjugated to another molecule, e.g., a peptide, hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent, etc.

The antisense oligonucleotide may comprise at least one modified base moiety which is selected from the group including but not limited to 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxymethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine.

The antisense oligonucleotide may also comprise at least one modified sugar moiety selected from the group including but not limited to arabinose, 2-fluoroarabinose, xylulose, and hexose.

In yet another embodiment, the antisense oligonucleotide comprises at least one modified phosphate backbone selected from the group consisting of a phosphorothioate, a phosphorodithioate, a phosphoramidothioate, a phosphoramidate, a phosphordiamidate, a methylphosphonate, an alkyl phosphotriester, and a formacetal or analog thereof.

In yet another embodiment, the antisense oligonucleotide is an  $\alpha$ -anomeric oligonucleotide. An  $\alpha$ -anomeric oligonucleotide forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual  $\beta$ -units, the strands run parallel to each other (Gautier, *et al.*, 1987, *Nucl. Acids Res.* 15:6625-6641). The oligonucleotide is a 2'-O-methylribonucleotide (Inoue, *et al.*, 1987, *Nucl. Acids Res.* 15:6131-6148), or a chimeric RNA-DNA analogue (Inoue, *et al.*, 1987, *FEBS Lett.* 215:327-330).

Oligonucleotides of the invention may be synthesized by standard methods known in the art, e.g., by use of an automated DNA synthesizer (such as are commercially available from Biosearch, Applied Biosystems, etc.). As examples, phosphorothioate oligonucleotides may be synthesized by the method of Stein, *et al.* (1988, *Nucl. Acids Res.* 16:3209), methylphosphonate oligonucleotides can be prepared by use of controlled pore glass polymer supports (Sarin, *et al.*, 1988, *Proc. Natl. Acad. Sci. U.S.A.* 85:7448-7451), etc.



The oligonucleotides described above can also be delivered to cells such that the antisense RNA or DNA may be expressed *in vivo* to inhibit production of the PRO polypeptide. When antisense DNA is used, oligodeoxyribonucleotides derived from the translation-initiation site, *e.g.*, between about -10 and +10 positions of the target gene nucleotide sequence, are preferred.

5 Antisense RNA or DNA molecules are generally at least about 5 bases in length, about 10 bases in length, about 15 bases in length, about 20 bases in length, about 25 bases in length, about 30 bases in length, about 35 bases in length, about 40 bases in length, about 45 bases in length, about 50 bases in length, about 55 bases in length, about 60 bases in length, about 65 bases in length, about 70 bases in length, about 75 bases in length, about 80 bases in length, about 85 bases in length, about 90 bases in length, about 95 bases in length, about 100 bases in length, or more.

Potential antagonists further include small molecules that bind to the active site, the receptor binding site, or growth factor or other relevant binding site of the PRO polypeptide, thereby blocking the normal biological activity of the PRO polypeptide. Examples of small molecules include, but are not limited to, small peptides or peptide-like molecules, preferably soluble peptides, and synthetic non-peptidyl organic or inorganic compounds.

15 Additional potential antagonists are ribozymes, which are enzymatic RNA molecules capable of catalyzing the specific cleavage of RNA. Ribozymes act by sequence-specific hybridization to the complementary target RNA, followed by endonucleolytic cleavage. Specific ribozyme cleavage sites within a potential RNA target can be identified by known techniques. For further details *see, e.g.*, Rossi, Current Biology, 4: 469-471 (1994), and PCT publication No. WO 97/33551 (published September 18, 1997).

20 While ribozymes that cleave mRNA at site specific recognition sequences can be used to destroy target gene mRNAs, the use of hammerhead ribozymes is preferred. Hammerhead ribozymes cleave mRNAs at locations dictated by flanking regions which form complementary base pairs with the target mRNA. The sole requirement is that the target mRNA have the following sequence of two bases: 5'-UG-3'. The construction and production of hammerhead ribozymes is well known in the art and is described more fully in Myers, 1995, *Molecular Biology and Biotechnology: A Comprehensive Desk Reference*, VCH Publishers, New York, (see especially Figure 4, page 833) and in Haseloff and Gerlach, 1988, *Nature*, 334:585-591, which is incorporated herein by reference in its entirety.

25 Preferably the ribozyme is engineered so that the cleavage recognition site is located near the 5' end of the target gene mRNA, *i.e.*, to increase efficiency and minimize the intracellular accumulation of non-functional mRNA transcripts.

30 The ribozymes of the present invention also include RNA endoribonucleases (hereinafter "Cech-type ribozymes") such as the one which occurs naturally in *Tetrahymena thermophila* (known as the IVS, or L-19 IVS RNA) and which has been extensively described by Thomas Cech and collaborators (Zaug, *et al.*, 1984, *Science*, 224:574-578; Zaug and Cech, 1986, *Science*, 231:470-475; Zaug, *et al.*, 1986, *Nature*, 324:429-433; published International patent application No. WO 88/04300 by University Patents Inc.; Been and Cech, 1986, *Cell*, 47:207-216). The Cech-type ribozymes have an eight base pair active site that hybridizes to a target RNA sequence

whereafter cleavage of the target RNA takes place. The invention encompasses those Cech-type ribozymes that target eight base-pair active site sequences that are present in the target gene.

As in the antisense approach, the ribozymes can be composed of modified oligonucleotides (e.g., for improved stability, targeting, etc.) and should be delivered to cells that express the target gene *in vivo*. A preferred method of delivery involves using a DNA construct "encoding" the ribozyme under the control of a strong constitutive pol III or pol II promoter, so that transfected cells will produce sufficient quantities of the ribozyme to destroy endogenous target gene messages and inhibit translation. Because ribozymes, unlike antisense molecules, are catalytic, a lower intracellular concentration is required for efficiency.

Nucleic acid molecules in triple-helix formation used to inhibit transcription should be single-stranded and composed of deoxynucleotides. The base composition of these oligonucleotides is designed such that it promotes triple-helix formation via Hoogsteen base-pairing rules, which generally require sizeable stretches of purines or pyrimidines on one strand of a duplex. For further details see, e.g., PCT publication No. WO 97/33551, *supra*.

These small molecules can be identified by any one or more of the screening assays discussed hereinabove and/or by any other screening techniques well known for those skilled in the art.

#### 5.2.4.10. Types of Cardiovascular, Endothelial, and Angiogenic Disorders to be Treated

The PRO polypeptides, or agonists or antagonists thereto, that have activity in the cardiovascular, angiogenic, and endothelial assays described herein, and/or whose gene product has been found to be localized to the cardiovascular system, are likely to have therapeutic uses in a variety of cardiovascular, endothelial, and angiogenic disorders, including systemic disorders that affect vessels, such as diabetes mellitus. Their therapeutic utility could include diseases of the arteries, capillaries, veins, and/or lymphatics. Examples of treatments hereunder include treating muscle wasting disease, treating osteoporosis, aiding in implant fixation to stimulate the growth of cells around the implant and therefore facilitate its attachment to its intended site, increasing IGF stability in tissues or in serum, if applicable, and increasing binding to the IGF receptor (since IGF has been shown *in vitro* to enhance human marrow erythroid and granulocytic progenitor cell growth).

The PRO polypeptides or agonists or antagonists thereto may also be employed to stimulate erythropoiesis or granulopoiesis, to stimulate wound healing or tissue regeneration and associated therapies concerned with re-growth of tissue, such as connective tissue, skin, bone, cartilage, muscle, lung, or kidney, to promote angiogenesis, to stimulate or inhibit migration of endothelial cells, and to proliferate the growth of vascular smooth muscle and endothelial cell production. The increase in angiogenesis mediated by the PRO polypeptide or agonist would be beneficial to ischemic tissues and to collateral coronary development in the heart subsequent to coronary stenosis. Antagonists are used to inhibit the action of such polypeptides, for example, to limit the production of excess connective tissue during wound healing or pulmonary fibrosis if the PRO polypeptide promotes such production. This would include treatment of acute myocardial infarction and heart failure.

Moreover, the present invention provides the treatment of cardiac hypertrophy, regardless of the underlying cause, by administering a therapeutically effective dose of the PRO polypeptide, or agonist or antagonist thereto. If the objective is the treatment of human patients, the PRO polypeptide preferably is recombinant human PRO

polypeptide (rhPRO polypeptide). The treatment for cardiac hypertrophy can be performed at any of its various stages, which may result from a variety of diverse pathologic conditions, including myocardial infarction, hypertension, hypertrophic cardiomyopathy, and valvular regurgitation. The treatment extends to all stages of the progression of cardiac hypertrophy, with or without structural damage of the heart muscle, regardless of the underlying cardiac disorder.

The decision of whether to use the molecule itself or an agonist thereof for any particular indication, as opposed to an antagonist to the molecule, would depend mainly on whether the molecule herein promotes cardiovascularization, genesis of endothelial cells, or angiogenesis or inhibits these conditions. For example, if the molecule promotes angiogenesis, an antagonist thereof would be useful for treatment of disorders where it is desired to limit or prevent angiogenesis. Examples of such disorders include vascular tumors such as haemangioma, tumor angiogenesis, neovascularization in the retina, choroid, or cornea, associated with diabetic retinopathy or premature infant retinopathy or macular degeneration and proliferative vitreoretinopathy, rheumatoid arthritis, Crohn's disease, atherosclerosis, ovarian hyperstimulation, psoriasis, endometriosis associated with neovascularization, restenosis subsequent to balloon angioplasty, scar tissue overproduction, for example, that seen in a keloid that forms after surgery, fibrosis after myocardial infarction, or fibrotic lesions associated with pulmonary fibrosis.

If, however, the molecule inhibits angiogenesis, it would be expected to be used directly for treatment of the above conditions.

On the other hand, if the molecule stimulates angiogenesis it would be used itself (or an agonist thereof) for indications where angiogenesis is desired such as peripheral vascular disease, hypertension, inflammatory vasculitides, Reynaud's disease and Reynaud's phenomenon, aneurysms, arterial restenosis, thrombophlebitis, lymphangitis, lymphedema, wound healing and tissue repair, ischemia reperfusion injury, angina, myocardial infarctions such as acute myocardial infarctions, chronic heart conditions, heart failure such as congestive heart failure, and osteoporosis.

If, however, the molecule inhibits angiogenesis, an antagonist thereof would be used for treatment of those conditions where angiogenesis is desired.

Specific types of diseases are described below, where the PRO polypeptide herein or agonists or antagonists thereof may serve as useful for vascular-related drug targeting or as therapeutic targets for the treatment or prevention of the disorders. Atherosclerosis is a disease characterized by accumulation of plaques of intimal thickening in arteries, due to accumulation of lipids, proliferation of smooth muscle cells, and formation of fibrous tissue within the arterial wall. The disease can affect large, medium, and small arteries in any organ. Changes in endothelial and vascular smooth muscle cell function are known to play an important role in modulating the accumulation and regression of these plaques.

Hypertension is characterized by raised vascular pressure in the systemic arterial, pulmonary arterial, or portal venous systems. Elevated pressure may result from or result in impaired endothelial function and/or vascular disease.

Inflammatory vasculitides include giant cell arteritis, Takayasu's arteritis, polyarteritis nodosa (including the microangiopathic form), Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, and a variety

of infectious-related vascular disorders (including Henoch-Schonlein purpura). Altered endothelial cell function has been shown to be important in these diseases.

Reynaud's disease and Reynaud's phenomenon are characterized by intermittent abnormal impairment of the circulation through the extremities on exposure to cold. Altered endothelial cell function has been shown to be important in this disease.

Aneurysms are saccular or fusiform dilatations of the arterial or venous tree that are associated with altered endothelial cell and/or vascular smooth muscle cells.

Arterial restenosis (restenosis of the arterial wall) may occur following angioplasty as a result of alteration in the function and proliferation of endothelial and vascular smooth muscle cells.

Thrombophlebitis and lymphangitis are inflammatory disorders of veins and lymphatics, respectively, that may result from, and/or in, altered endothelial cell function. Similarly, lymphedema is a condition involving impaired lymphatic vessels resulting from endothelial cell function.

The family of benign and malignant vascular tumors are characterized by abnormal proliferation and growth of cellular elements of the vascular system. For example, lymphangiomas are benign tumors of the lymphatic system that are congenital, often cystic, malformations of the lymphatics that usually occur in newborns. Cystic tumors tend to grow into the adjacent tissue. Cystic tumors usually occur in the cervical and axillary region. They can also occur in the soft tissue of the extremities. The main symptoms are dilated, sometimes reticular, structured lymphatics and lymphocysts surrounded by connective tissue. Lymphangiomas are assumed to be caused by improperly connected embryonic lymphatics or their deficiency. The result is impaired local lymph drainage. Griener *et al.*, Lymphology, 4: 140-144 (1971).

Another use for the PRO polypeptides herein or agonists or antagonists thereto is in the prevention of tumor angiogenesis, which involves vascularization of a tumor to enable it to growth and/or metastasize. This process is dependent on the growth of new blood vessels. Examples of neoplasms and related conditions that involve tumor angiogenesis include breast carcinomas, lung carcinomas, gastric carcinomas, esophageal carcinomas, colorectal carcinomas, liver carcinomas, ovarian carcinomas, thecomas, arrhenoblastomas, cervical carcinomas, endometrial carcinoma, endometrial hyperplasia, endometriosis, fibrosarcomas, choriocarcinoma, head and neck cancer, nasopharyngeal carcinoma, laryngeal carcinomas, hepatoblastoma, Kaposi's sarcoma, melanoma, skin carcinomas, hemangioma, cavernous hemangioma, hemangioblastoma, pancreas carcinomas, retinoblastoma, astrocytoma, glioblastoma, Schwannoma, oligodendroglioma, medulloblastoma, neuroblastomas, rhabdomyosarcoma, osteogenic sarcoma, leiomyosarcomas, urinary tract carcinomas, thyroid carcinomas, Wilm's tumor, renal cell carcinoma, prostate carcinoma, abnormal vascular proliferation associated with phakomatoses, edema (such as that associated with brain tumors), and Meigs' syndrome.

Age-related macular degeneration (AMD) is a leading cause of severe visual loss in the elderly population. The exudative form of AMD is characterized by choroidal neovascularization and retinal pigment epithelial cell detachment. Because choroidal neovascularization is associated with a dramatic worsening in prognosis, the PRO polypeptide or agonist or antagonist thereto is expected to be useful in reducing the severity of AMD.

Healing of trauma such as wound healing and tissue repair is also a targeted use for the PRO polypeptides herein or their agonists or antagonists. Formation and regression of new blood vessels is essential for tissue healing and repair. This category includes bone, cartilage, tendon, ligament, and/or nerve tissue growth or regeneration, as well as wound healing and tissue repair and replacement, and in the treatment of burns, incisions, and ulcers.

5 A PRO polypeptide or agonist or antagonist thereof that induces cartilage and/or bone growth in circumstances where bone is not normally formed has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Such a preparation employing a PRO polypeptide or agonist or antagonist thereof may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. *De novo* bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma-  
10 induced, or oncologic, resection-induced craniofacial defects, and also is useful in cosmetic plastic surgery.

PRO polypeptides or agonists or antagonists thereto may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds, and the like.

15 It is expected that a PRO polypeptide or agonist or antagonist thereto may also exhibit activity for generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, or endothelium), muscle (smooth, skeletal, or cardiac), and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation of fibrotic scarring to allow normal tissue to regenerate.

20 A PRO polypeptide herein or agonist or antagonist thereto may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokine damage. Also, the PRO polypeptide or agonist or antagonist thereto may be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells, or for inhibiting the growth of tissues described above.

25 A PRO polypeptide or agonist or antagonist thereto may also be used in the treatment of periodontal diseases and in other tooth-repair processes. Such agents may provide an environment to attract bone-forming cells, stimulate growth of bone-forming cells, or induce differentiation of progenitors of bone-forming cells. A PRO polypeptide herein or an agonist or an antagonist thereto may also be useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes, since blood  
30 vessels play an important role in the regulation of bone turnover and growth.

35 Another category of tissue regeneration activity that may be attributable to the PRO polypeptide herein or agonist or antagonist thereto is tendon/ligament formation. A protein that induces tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed has application in the healing of tendon or ligament tears, deformities, and other tendon or ligament defects in humans and other animals. Such a preparation may have prophylactic use in preventing damage to tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. *De novo* tendon/ligament-like tissue formation induced by a composition of the PRO polypeptide herein or

agonist or antagonist thereto contributes to the repair of congenital, trauma-induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions herein may provide an environment to attract tendon- or ligament-forming cells, stimulate growth of tendon- or ligament-forming cells, induce differentiation of progenitors of tendon- or ligament-forming cells, or induce growth of tendon/ligament cells or progenitors *ex vivo* for return *in vivo* to effect tissue repair. The compositions herein may also be useful in the treatment of tendinitis, carpal tunnel syndrome, and other tendon or ligament defects. The compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in the art.

The PRO polypeptide or its agonist or antagonist may also be useful for proliferation of neural cells and for regeneration of nerve and brain tissue, *i.e.*, for the treatment of central and peripheral nervous system disease and neuropathies, as well as mechanical and traumatic disorders, that involve degeneration, death, or trauma to neural cells or nerve tissue. More specifically, a PRO polypeptide or its agonist or antagonist may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions that may be treated in accordance with the present invention include mechanical and traumatic disorders, such as spinal cord disorders, head trauma, and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a PRO polypeptide herein or agonist or antagonist thereto.

Ischemia-reperfusion injury is another indication. Endothelial cell dysfunction may be important in both the initiation of, and in regulation of the sequelae of events that occur following ischemia-reperfusion injury.

Rheumatoid arthritis is a further indication. Blood vessel growth and targeting of inflammatory cells through the vasculature is an important component in the pathogenesis of rheumatoid and sero-negative forms of arthritis.

A PRO polypeptide or its agonist or antagonist may also be administered prophylactically to patients with cardiac hypertrophy, to prevent the progression of the condition, and avoid sudden death, including death of asymptomatic patients. Such preventative therapy is particularly warranted in the case of patients diagnosed with massive left ventricular cardiac hypertrophy (a maximal wall thickness of 35 mm or more in adults, or a comparable value in children), or in instances when the hemodynamic burden on the heart is particularly strong.

A PRO polypeptide or its agonist or antagonist may also be useful in the management of atrial fibrillation, which develops in a substantial portion of patients diagnosed with hypertrophic cardiomyopathy.

Further indications include angina, myocardial infarctions such as acute myocardial infarctions, and heart failure such as congestive heart failure. Additional non-neoplastic conditions include psoriasis, diabetic and other proliferative retinopathies including retinopathy of prematurity, retrolental fibroplasia, neovascular glaucoma, thyroid hyperplasias (including Grave's disease), corneal and other tissue transplantation, chronic inflammation, lung inflammation, nephrotic syndrome, preeclampsia, ascites, pericardial effusion (such as that associated with pericarditis), and pleural effusion.

In view of the above, the PRO polypeptides or agonists or antagonists thereof described herein, which are shown to alter or impact endothelial cell function, proliferation, and/or form, are likely to play an important role in the etiology and pathogenesis of many or all of the disorders noted above, and as such can serve as therapeutic targets to augment or inhibit these processes or for vascular-related drug targeting in these disorders.

#### 5.2.4.11. Administration Protocols, Schedules, Doses, and Formulations

The molecules herein and agonists and antagonists thereto are pharmaceutically useful as a prophylactic and therapeutic agent for various disorders and diseases as set forth above.

Therapeutic compositions of the PRO polypeptides or agonists or antagonists are prepared for storage by mixing the desired molecule having the appropriate degree of purity with optional pharmaceutically acceptable carriers, excipients, or stabilizers (Remington's Pharmaceutical Sciences, 16th edition, Osol, A. ed. (1980)), in the form of lyophilized formulations or aqueous solutions. Acceptable carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrans; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (*e.g.*, Zn-protein complexes); and/or non-ionic surfactants such as TWEEN™, PLURONICS™ or polyethylene glycol (PEG).

Additional examples of such carriers include ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts, or electrolytes such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, and polyethylene glycol. Carriers for topical or gel-based forms of agonist or antagonist include polysaccharides such as sodium carboxymethylcellulose or methylcellulose, polyvinylpyrrolidone, polyacrylates, polyoxyethylene-polyoxypropylene-block polymers, polyethylene glycol, and wood wax alcohols. For all administrations, conventional depot forms are suitably used. Such forms include, for example, microcapsules, nano-capsules, liposomes, plasters, inhalation forms, nose sprays, sublingual tablets, and sustained-release preparations. The PRO polypeptides or agonists or antagonists will typically be formulated in such vehicles at a concentration of about 0.1 mg/ml to 100 mg/ml.

Another formulation comprises incorporating a PRO polypeptide or agonist or antagonist thereof into formed articles. Such articles can be used in modulating endothelial cell growth and angiogenesis. In addition, tumor invasion and metastasis may be modulated with these articles.

PRO polypeptides or agonists or antagonists to be used for *in vivo* administration must be sterile. This is readily accomplished by filtration through sterile filtration membranes, prior to or following lyophilization and reconstitution. PRO polypeptides ordinarily will be stored in lyophilized form or in solution if administered systemically. If in lyophilized form, the PRO polypeptide or agonist or antagonist thereto is typically formulated in combination with other ingredients for reconstitution with an appropriate diluent at the time for use. An example of a liquid formulation of a PRO polypeptide or agonist or antagonist is a sterile, clear, colorless unpreserved solution filled in a single-dose vial for subcutaneous injection. Preserved pharmaceutical compositions suitable for repeated use may contain, for example, depending mainly on the indication and type of polypeptide:

- a) PRO polypeptide or agonist or antagonist thereto;
- b) a buffer capable of maintaining the pH in a range of maximum stability of the polypeptide or other molecule in solution, preferably about 4-8;
- c) a detergent/surfactant primarily to stabilize the polypeptide or molecule against agitation-induced aggregation;
- d) an isotonifier;
- e) a preservative selected from the group of phenol, benzyl alcohol and a benzethonium halide, *e.g.*, chloride; and
- f) water.

If the detergent employed is non-ionic, it may, for example, be polysorbates (*e.g.*, POLYSORBATE™ (TWEEN™) 20, 80, etc.) or poloxamers (*e.g.*, POLOXAMER™ 188). The use of non-ionic surfactants permits the formulation to be exposed to shear surface stresses without causing denaturation of the polypeptide. Further, such surfactant-containing formulations may be employed in aerosol devices such as those used in a pulmonary dosing, and needleless jet injector guns (*see, e.g.*, EP 257,956).

An isotonifier may be present to ensure isotonicity of a liquid composition of the PRO polypeptide or agonist or antagonist thereto, and includes polyhydric sugar alcohols, preferably trihydric or higher sugar alcohols, such as glycerin, erythritol, arabitol, xylitol, sorbitol, and mannitol. These sugar alcohols can be used alone or in combination. Alternatively, sodium chloride or other appropriate inorganic salts may be used to render the solutions isotonic.

The buffer may, for example, be an acetate, citrate, succinate, or phosphate buffer depending on the pH desired. The pH of one type of liquid formulation of this invention is buffered in the range of about 4 to 8, preferably about physiological pH.

The preservatives phenol, benzyl alcohol and benzethonium halides, *e.g.*, chloride, are known antimicrobial agents that may be employed.

Therapeutic PRO polypeptide compositions generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle. The formulations are preferably administered as repeated intravenous (*i.v.*), subcutaneous (*s.c.*), or intramuscular (*i.m.*) injections, or as aerosol formulations suitable for intranasal or intrapulmonary delivery (for intrapulmonary delivery *see, e.g.*, EP 257,956).



PRO polypeptides can also be administered in the form of sustained-released preparations. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the protein, which matrices are in the form of shaped articles, *e.g.*, films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (*e.g.*, poly(2-hydroxyethyl-methacrylate) as described by Langer *et al.*, J. Biomed. Mater. Res., **15**: 167-277 (1981) and Langer, Chem. Tech., **12**: 98-105 (1982) or poly(vinylalcohol)), polylactides (U.S. Patent No. 3,773,919, EP 58,481), copolymers of L-glutamic acid and gamma ethyl-L-glutamate (Sidman *et al.*, Biopolymers, **22**: 547-556 (1983)), non-degradable ethylene-vinyl acetate (Langer *et al.*, *supra*), degradable lactic acid-glycolic acid copolymers such as the Lupron Depot™ (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)-3-hydroxybutyric acid (EP 133,988).

While polymers such as ethylene-vinyl acetate and lactic acid-glycolic acid enable release of molecules for over 100 days, certain hydrogels release proteins for shorter time periods. When encapsulated proteins remain in the body for a long time, they may denature or aggregate as a result of exposure to moisture at 37°C, resulting in a loss of biological activity and possible changes in immunogenicity. Rational strategies can be devised for protein stabilization depending on the mechanism involved. For example, if the aggregation mechanism is discovered to be intermolecular S-S bond formation through thio-disulfide interchange, stabilization may be achieved by modifying sulfhydryl residues, lyophilizing from acidic solutions, controlling moisture content, using appropriate additives, and developing specific polymer matrix compositions.

Sustained-release PRO polypeptide compositions also include liposomally entrapped PRO polypeptides. Liposomes containing the PRO polypeptide are prepared by methods known *per se*: DE 3,218,121; Epstein *et al.*, Proc. Natl. Acad. Sci. USA, **82**: 3688-3692 (1985); Hwang *et al.*, Proc. Natl. Acad. Sci. USA, **77**: 4030-4034 (1980); EP 52,322; EP 36,676; EP 88,046; EP 143,949; EP 142,641; Japanese patent application 83-118008; U.S. Patent Nos. 4,485,045 and 4,544,545; and EP 102,324. Ordinarily the liposomes are of the small (about 200-800 Angstroms) unilamellar type in which the lipid content is greater than about 30 mol. % cholesterol, the selected proportion being adjusted for the optimal therapy.

The therapeutically effective dose of a PRO polypeptide or agonist or antagonist thereto will, of course, vary depending on such factors as the pathological condition to be treated (including prevention), the method of administration, the type of compound being used for treatment, any co-therapy involved, the patient's age, weight, general medical condition, medical history, etc., and its determination is well within the skill of a practicing physician. Accordingly, it will be necessary for the therapist to titer the dosage and modify the route of administration as required to obtain the maximal therapeutic effect. If the PRO polypeptide has a narrow host range, for the treatment of human patients formulations comprising human PRO polypeptide, more preferably native-sequence human PRO polypeptide, are preferred. The clinician will administer the PRO polypeptide until a dosage is reached that achieves the desired effect for treatment of the condition in question. For example, if the objective is the treatment of CHF, the amount would be one that inhibits the progressive cardiac hypertrophy associated with this condition. The progress of this therapy is easily monitored by echo cardiography. Similarly, in patients with hypertrophic cardiomyopathy, the PRO polypeptide can be administered on an empirical basis.

With the above guidelines, the effective dose generally is within the range of from about 0.001 to about 1.0 mg/kg, more preferably about 0.01-1.0 mg/kg, most preferably about 0.01-0.1 mg/kg.

For non-oral use in treating human adult hypertension, it is advantageous to administer the PRO polypeptide in the form of an injection at about 0.01 to 50 mg, preferably about 0.05 to 20 mg, most preferably 1 to 20 mg, per kg body weight, 1 to 3 times daily by intravenous injection. For oral administration, a molecule based on the PRO polypeptide is preferably administered at about 5 mg to 1 g, preferably about 10 to 100 mg, per kg body weight, 1 to 3 times daily. It should be appreciated that endotoxin contamination should be kept minimally at a safe level, for example, less than 0.5 ng/mg protein. Moreover, for human administration, the formulations preferably meet sterility, pyrogenicity, general safety, and purity as required by FDA Office and Biologics standards.

The dosage regimen of a pharmaceutical composition containing the PRO polypeptide to be used in tissue regeneration will be determined by the attending physician considering various factors that modify the action of the polypeptides, *e.g.*, amount of tissue weight desired to be formed, the site of damage, the condition of the damaged tissue, the size of a wound, type of damaged tissue (*e.g.*, bone), the patient's age, sex, and diet, the severity of any infection, time of administration, and other clinical factors. The dosage may vary with the type of matrix used in the reconstitution and with inclusion of other proteins in the pharmaceutical composition. For example, the addition of other known growth factors, such as IGF-I, to the final composition may also affect the dosage. Progress can be monitored by periodic assessment of tissue/bone growth and/or repair, for example, X-rays, histomorphometric determinations, and tetracycline labeling.

The route of PRO polypeptide or antagonist or agonist administration is in accord with known methods, *e.g.*, by injection or infusion by intravenous, intramuscular, intracerebral, intraperitoneal, intracerebrospinal, subcutaneous, intraocular, intraarticular, intrasynovial, intrathecal, oral, topical, or inhalation routes, or by sustained-release systems as noted below. The PRO polypeptide or agonist or antagonists thereof also are suitably administered by intratumoral, peritumoral, intralesional, or perilesional routes, to exert local as well as systemic therapeutic effects. The intraperitoneal route is expected to be particularly useful, for example, in the treatment of ovarian tumors.

If a peptide or small molecule is employed as an antagonist or agonist, it is preferably administered orally or non-orally in the form of a liquid or solid to mammals.

Examples of pharmacologically acceptable salts of molecules that form salts and are useful hereunder include alkali metal salts (*e.g.*, sodium salt, potassium salt), alkaline earth metal salts (*e.g.*, calcium salt, magnesium salt), ammonium salts, organic base salts (*e.g.*, pyridine salt, triethylamine salt), inorganic acid salts (*e.g.*, hydrochloride, sulfate, nitrate), and salts of organic acid (*e.g.*, acetate, oxalate, p-toluenesulfonate).

For compositions herein that are useful for bone, cartilage, tendon, or ligament regeneration, the therapeutic method includes administering the composition topically, systemically, or locally as an implant or device. When administered, the therapeutic composition for use is in a pyrogen-free, physiologically acceptable form. Further, the composition may desirably be encapsulated or injected in a viscous form for delivery to the site of bone, cartilage, or tissue damage. Topical administration may be suitable for wound healing and tissue repair. Preferably, for bone and/or cartilage formation, the composition would include a matrix capable of delivering the

protein-containing composition to the site of bone and/or cartilage damage, providing a structure for the developing bone and cartilage and preferably capable of being resorbed into the body. Such matrices may be formed of materials presently in use for other implanted medical applications.

5 The choice of matrix material is based on biocompatibility, biodegradability, mechanical properties, cosmetic appearance, and interface properties. The particular application of the compositions will define the appropriate formulation. Potential matrices for the compositions may be biodegradable and chemically defined calcium sulfate, tricalcium phosphate, hydroxyapatite, polylactic acid, polyglycolic acid, and polyanhydrides. Other potential materials are biodegradable and biologically well-defined, such as bone or dermal collagen. Further matrices are comprised of pure proteins or extracellular matrix components. Other potential matrices are 10 nonbiodegradable and chemically defined, such as sintered hydroxyapatite, bioglass, aluminates, or other ceramics. Matrices may be comprised of combinations of any of the above-mentioned types of material, such as polylactic acid and hydroxyapatite or collagen and tricalcium phosphate. The bioceramics may be altered in composition, such as in calcium-aluminate-phosphate and processing to alter pore size, particle size, particle shape, and biodegradability.

15 One specific embodiment is a 50:50 (mole weight) copolymer of lactic acid and glycolic acid in the form of porous particles having diameters ranging from 150 to 800 microns. In some applications, it will be useful to utilize a sequestering agent, such as carboxymethyl cellulose or autologous blood clot, to prevent the polypeptide compositions from disassociating from the matrix.

20 One suitable family of sequestering agents is cellulosic materials such as alkylcelluloses (including hydroxyalkylcelluloses), including methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, and carboxymethylcellulose, one preferred being cationic salts of carboxymethylcellulose (CMC). Other preferred sequestering agents include hyaluronic acid, sodium alginate, poly(ethylene glycol), polyoxyethylene oxide, carboxyvinyl polymer, and poly(vinyl alcohol). The amount of sequestering agent useful herein is 0.5-20 wt%, preferably 1-10 wt%, based on total formulation weight, which 25 represents the amount necessary to prevent desorption of the polypeptide (or its antagonist) from the polymer matrix and to provide appropriate handling of the composition, yet not so much that the progenitor cells are prevented from infiltrating the matrix, thereby providing the polypeptide (or its antagonist) the opportunity to assist the osteogenic activity of the progenitor cells.

#### 5.2.4.12. Combination Therapies

30 The effectiveness of the PRO polypeptide or an agonist or antagonist thereof in preventing or treating the disorder in question may be improved by administering the active agent serially or in combination with another agent that is effective for those purposes, either in the same composition or as separate compositions.

For example, for treatment of cardiac hypertrophy, PRO polypeptide therapy can be combined with the administration of inhibitors of known cardiac myocyte hypertrophy factors, e.g., inhibitors of  $\alpha$ -adrenergic agonists 35 such as phenylephrine; endothelin-1 inhibitors such as BOSENTAN<sup>TM</sup> and MOXONODIN<sup>TM</sup>; inhibitors to CT-1

(U.S. Pat. No. 5,679,545); inhibitors to LIF; ACE inhibitors; des-aspartate-angiotensin I inhibitors (U.S. Pat. No. 5,773,415), and angiotensin II inhibitors.

For treatment of cardiac hypertrophy associated with hypertension, the PRO polypeptide can be administered in combination with  $\beta$ -adrenergic receptor blocking agents, *e.g.*, propranolol, timolol, tertalolol, carteolol, nadolol, betaxolol, penbutolol, acetobutolol, atenolol, metoprolol, or carvedilol; ACE inhibitors, *e.g.*, quinapril, captopril, enalapril, ramipril, benazepril, fosinopril, or lisinopril; diuretics, *e.g.*, chlorothiazide, hydrochlorothiazide, hydroflumethazide, methylchlorothiazide, benzthiazide, dichlorphenamide, acetazolamide, or indapamide; and/or calcium channel blockers, *e.g.*, diltiazem, nifedipine, verapamil, or nicardipine. Pharmaceutical compositions comprising the therapeutic agents identified herein by their generic names are commercially available, and are to be administered following the manufacturers' instructions for dosage, administration, adverse effects, contraindications, etc. *See, e.g., Physicians' Desk Reference* (Medical Economics Data Production Co.: Montvale, N.J., 1997), 51th Edition.

Preferred candidates for combination therapy in the treatment of hypertrophic cardiomyopathy are  $\beta$ -adrenergic-blocking drugs (*e.g.*, propranolol, timolol, tertalolol, carteolol, nadolol, betaxolol, penbutolol, acetobutolol, atenolol, metoprolol, or carvedilol), verapamil, diltiazem, or diltiazem. Treatment of hypertrophy associated with high blood pressure may require the use of antihypertensive drug therapy, using calcium channel blockers, *e.g.*, diltiazem, nifedipine, verapamil, or nicardipine;  $\beta$ -adrenergic blocking agents; diuretics, *e.g.*, chlorothiazide, hydrochlorothiazide, hydroflumethazide, methylchlorothiazide, benzthiazide, dichlorphenamide, acetazolamide, or indapamide; and/or ACE-inhibitors, *e.g.*, quinapril, captopril, enalapril, ramipril, benazepril, fosinopril, or lisinopril.

For other indications, PRO polypeptides or their agonists or antagonists may be combined with other agents beneficial to the treatment of the bone and/or cartilage defect, wound, or tissue in question. These agents include various growth factors such as EGF, PDGF, TGF- $\alpha$  or TGF- $\beta$ , IGF, FGF, and CTGF.

In addition, PRO polypeptides or their agonists or antagonists used to treat cancer may be combined with cytotoxic, chemotherapeutic, or growth-inhibitory agents as identified above. Also, for cancer treatment, the PRO polypeptide or agonist or antagonist thereof is suitably administered serially or in combination with radiological treatments, whether involving irradiation or administration of radioactive substances.

The effective amounts of the therapeutic agents administered in combination with the PRO polypeptide or agonist or antagonist thereof will be at the physician's or veterinarian's discretion. Dosage administration and adjustment is done to achieve maximal management of the conditions to be treated. For example, for treating hypertension, these amounts ideally take into account use of diuretics or digitalis, and conditions such as hyper- or hypotension, renal impairment, etc. The dose will additionally depend on such factors as the type of the therapeutic agent to be used and the specific patient being treated. Typically, the amount employed will be the same dose as that used, if the given therapeutic agent is administered without the PRO polypeptide.

#### 5.2.4.13. Articles of Manufacture

An article of manufacture such as a kit containing the PRO polypeptide or agonists or antagonists thereof useful for the diagnosis or treatment of the disorders described above comprises at least a container and a label. Suitable containers include, for example, bottles, vials, syringes, and test tubes. The containers may be formed from a variety of materials such as glass or plastic. The container holds a composition that is effective for diagnosing or treating the condition and may have a sterile access port (for example, the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). The active agent in the composition is the PRO polypeptide or an agonist or antagonist thereto. The label on, or associated with, the container indicates that the composition is used for diagnosing or treating the condition of choice. The article of manufacture may further comprise a second container comprising a pharmaceutically-acceptable buffer, such as phosphate-buffered saline, Ringer's solution, and dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, syringes, and package inserts with instructions for use. The article of manufacture may also comprise a second or third container with another active agent as described above.

#### 5.2.5. Antibodies

Some of the most promising drug candidates according to the present invention are antibodies and antibody fragments that may inhibit the production or the gene product of the genes identified herein and/or reduce the activity of the gene products.

##### 5.2.5.1. Polyclonal Antibodies

Methods of preparing polyclonal antibodies are known to the skilled artisan. Polyclonal antibodies can be raised in a mammal, for example, by one or more injections of an immunizing agent and, if desired, an adjuvant. Typically, the immunizing agent and/or adjuvant will be injected in the mammal by multiple subcutaneous or intraperitoneal injections. The immunizing agent may include the PRO polypeptide or a fusion protein thereof. It may be useful to conjugate the immunizing agent to a protein known to be immunogenic in the mammal being immunized. Examples of such immunogenic proteins include, but are not limited to, keyhole limpet hemocyanin, serum albumin, bovine thyroglobulin, and soybean trypsin inhibitor. Examples of adjuvants that may be employed include Freund's complete adjuvant and MPL-TDM adjuvant (monophosphoryl Lipid A or synthetic trehalose dicorynomycolate). The immunization protocol may be selected by one skilled in the art without undue experimentation.

##### 5.2.5.2. Monoclonal Antibodies

The anti-PRO antibodies may, alternatively, be monoclonal antibodies. Monoclonal antibodies may be prepared using hybridoma methods, such as those described by Kohler and Milstein, *Nature*, 256:495 (1975). In a hybridoma method, a mouse, hamster, or other appropriate host animal is typically immunized with an

immunizing agent to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the immunizing agent. Alternatively, the lymphocytes may be immunized *in vitro*.

The immunizing agent will typically include the PRO polypeptide or a fusion protein thereof. Generally, either peripheral blood lymphocytes ("PBLs") are used if cells of human origin are desired, or spleen cells or lymph node cells are used if non-human mammalian sources are desired. The lymphocytes are then fused with an immortalized cell line using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell. Goding, Monoclonal Antibodies: Principles and Practice (New York: Academic Press, 1986), pp. 59-103. Immortalized cell lines are usually transformed mammalian cells, particularly myeloma cells of rodent, bovine, and human origin. Usually, rat or mouse myeloma cell lines are employed. The hybridoma cells may be cultured in a suitable culture medium that preferably contains one or more substances that inhibit the growth or survival of the unfused, immortalized cells. For example, if the parental cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and thymidine ("HAT medium"), which substances prevent the growth of HGPRT-deficient cells.

Preferred immortalized cell lines are those that fuse efficiently, support stable high-level expression of antibody by the selected antibody-producing cells, and are sensitive to a medium such as HAT medium. More preferred immortalized cell lines are murine myeloma lines, which can be obtained, for instance, from the Salk Institute Cell Distribution Center, San Diego, California and the American Type Culture Collection, Manassas, Virginia. Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of human monoclonal antibodies. Kozbor, J. Immunol., 133:3001 (1984); Brodeur *et al.*, Monoclonal Antibody Production Techniques and Applications (Marcel Dekker, Inc.: New York, 1987) pp. 51-63.

The culture medium in which the hybridoma cells are cultured can then be assayed for the presence of monoclonal antibodies directed against the PRO polypeptide. Preferably, the binding specificity of monoclonal antibodies produced by the hybridoma cells is determined by immunoprecipitation or by an *in vitro* binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunoabsorbent assay (ELISA). Such techniques and assays are known in the art. The binding affinity of the monoclonal antibody can, for example, be determined by the Scatchard analysis of Munson and Pollard, Anal. Biochem., 107:220 (1980).

After the desired hybridoma cells are identified, the clones may be subcloned by limiting dilution procedures and grown by standard methods. Goding, *supra*. Suitable culture media for this purpose include, for example, Dulbecco's Modified Eagle's Medium and RPMI-1640 medium. Alternatively, the hybridoma cells may be grown *in vivo* as ascites in a mammal.

The monoclonal antibodies secreted by the subclones may be isolated or purified from the culture medium or ascites fluid by conventional immunoglobulin purification procedures such as, for example, protein A-Sepharose, hydroxylapatite chromatography, gel electrophoresis, dialysis, or affinity chromatography.

The monoclonal antibodies may also be made by recombinant DNA methods, such as those described in U.S. Patent No. 4,816,567. DNA encoding the monoclonal antibodies of the invention can be readily isolated and sequenced using conventional procedures (*e.g.*, by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of murine antibodies). The hybridoma cells of the

invention serve as a preferred source of such DNA. Once isolated, the DNA may be placed into expression vectors, which are then transfected into host cells such as simian COS cells, Chinese hamster ovary (CHO) cells, or myeloma cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. The DNA also may be modified, for example, by substituting the coding sequence for human heavy- and light-chain constant domains in place of the homologous murine sequences (U.S. Patent No. 4,816,567; Morrison *et al.*, *supra*) or by covalently joining to the immunoglobulin coding sequence all or part of the coding sequence for a non-immunoglobulin polypeptide. Such a non-immunoglobulin polypeptide can be substituted for the constant domains of an antibody of the invention, or can be substituted for the variable domains of one antigen-combining site of an antibody of the invention to create a chimeric bivalent antibody.

The antibodies may be monovalent antibodies. Methods for preparing monovalent antibodies are well known in the art. For example, one method involves recombinant expression of immunoglobulin light chain and modified heavy chain. The heavy chain is truncated generally at any point in the Fc region so as to prevent heavy-chain crosslinking. Alternatively, the relevant cysteine residues are substituted with another amino acid residue or are deleted so as to prevent crosslinking.

*In vitro* methods are also suitable for preparing monovalent antibodies. Digestion of antibodies to produce fragments thereof, particularly Fab fragments, can be accomplished using routine techniques known in the art.

#### 5.2.5.3. Human and Humanized Antibodies

The anti-PRO antibodies may further comprise humanized antibodies or human antibodies. Humanized forms of non-human (*e.g.*, murine) antibodies are chimeric immunoglobulins, immunoglobulin chains, or fragments thereof (such as Fv, Fab, Fab', F(ab')<sub>2</sub>, or other antigen-binding subsequences of antibodies) that contain minimal sequence derived from non-human immunoglobulin. Humanized antibodies include human immunoglobulins (recipient antibody) in which residues from a CDR of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat, or rabbit having the desired specificity, affinity, and capacity. In some instances, Fv framework residues of the human immunoglobulin are replaced by corresponding non-human residues. Humanized antibodies may also comprise residues that are found neither in the recipient antibody nor in the imported CDR or framework sequences. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin, and all or substantially all of the FR regions are those of a human immunoglobulin consensus sequence. The humanized antibody preferably also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. Jones *et al.*, Nature, 321: 522-525 (1986); Riechmann *et al.*, Nature, 332: 323-329 (1988); Presta, Curr. Op. Struct. Biol., 2:593-596 (1992).

Methods for humanizing non-human antibodies are well known in the art. Generally, a humanized antibody has one or more amino acid residues introduced into it from a source that is non-human. These non-human amino acid residues are often referred to as "import" residues, which are typically taken from an "import" variable domain. Humanization can be essentially performed following the method of Winter and co-workers (Jones *et al.*, Nature, 321: 522-525 (1986); Riechmann *et al.*, Nature, 332: 323-327 (1988); Verhoeyen *et al.*, Science, 239: 1534-

1536 (1988)), by substituting rodent CDRs or CDR sequences for the corresponding sequences of a human antibody. Accordingly, such "humanized" antibodies are chimeric antibodies (U.S. Patent No. 4,816,567), wherein substantially less than an intact human variable domain has been substituted by the corresponding sequence from a non-human species. In practice, humanized antibodies are typically human antibodies in which some CDR residues and possibly some FR residues are substituted by residues from analogous sites in rodent antibodies.

Human antibodies can also be produced using various techniques known in the art, including phage display libraries. Hoogenboom and Winter, *J. Mol. Biol.*, 227: 381 (1991); Marks *et al.*, *J. Mol. Biol.*, 222: 581 (1991). The techniques of Cole *et al.* and Boerner *et al.* are also available for the preparation of human monoclonal antibodies. Cole *et al.*, *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, p. 77 (1985) and Boerner *et al.*, *J. Immunol.*, 147(1): 86-95 (1991). Similarly, human antibodies can be made by introducing human immunoglobulin loci into transgenic animals, *e.g.*, mice in which the endogenous immunoglobulin genes have been partially or completely inactivated. Upon challenge, human antibody production is observed that closely resembles that seen in humans in all respects, including gene rearrangement, assembly, and antibody repertoire. This approach is described, for example, in U.S. Patent Nos. 5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; and 5,661,016, and in the following scientific publications: Marks *et al.*, *Bio/Technology*, 10: 779-783 (1992); Lonberg *et al.*, *Nature*, 368: 856-859 (1994); Morrison, *Nature*, 368: 812-813 (1994); Fishwild *et al.*, *Nature Biotechnology*, 14: 845-851 (1996); Neuberger, *Nature Biotechnology*, 14: 826 (1996); Lonberg and Huszar, *Intern. Rev. Immunol.*, 13: 65-93 (1995).

#### 5.2.5.4. Bispecific Antibodies

Bispecific antibodies are monoclonal, preferably human or humanized, antibodies that have binding specificities for at least two different antigens. In the present case, one of the binding specificities is for the PRO polypeptide, the other one is for any other antigen, and preferably for a cell-surface protein or receptor or receptor subunit.

Methods for making bispecific antibodies are known in the art. Traditionally, the recombinant production of bispecific antibodies is based on the co-expression of two immunoglobulin heavy-chain/light-chain pairs, where the two heavy chains have different specificities. Milstein and Cuello, *Nature*, 305: 537-539 (1983). Because of the random assortment of immunoglobulin heavy and light chains, these hybridomas (quadromas) produce a potential mixture of ten different antibody molecules, of which only one has the correct bispecific structure. The purification of the correct molecule is usually accomplished by affinity chromatography steps. Similar procedures are disclosed in WO 93/08829, published 13 May 1993, and in Traunecker *et al.*, *EMBO J.*, 10: 3655-3659 (1991).

Antibody variable domains with the desired binding specificities (antibody-antigen combining sites) can be fused to immunoglobulin constant-domain sequences. The fusion preferably is with an immunoglobulin heavy-chain constant domain, comprising at least part of the hinge, CH2, and CH3 regions. It is preferred to have the first heavy-chain constant region (CH1) containing the site necessary for light-chain binding present in at least one of the fusions. DNAs encoding the immunoglobulin heavy-chain fusions and, if desired, the immunoglobulin light chain, are inserted into separate expression vectors, and are co-transfected into a suitable host organism. For further



details of generating bispecific antibodies, *see*, for example, Suresh *et al.*, Methods in Enzymology, **121**: 210 (1986).

#### 5.2.5.5. Heteroconjugate Antibodies

Heteroconjugate antibodies are composed of two covalently joined antibodies. Such antibodies have, for example, been proposed to target immune-system cells to unwanted cells (U.S. Patent No. 4,676,980), and for treatment of HIV infection. WO 91/00360; WO 92/200373; EP 03089. It is contemplated that the antibodies may be prepared *in vitro* using known methods in synthetic protein chemistry, including those involving crosslinking agents. For example, immunotoxins may be constructed using a disulfide-exchange reaction or by forming a thioether bond. Examples of suitable reagents for this purpose include iminothiolate and methyl-4-mercaptobutyrimidate and those disclosed, for example, in U.S. Patent No. 4,676,980.

#### 5.2.5.6. Effector Function Engineering

It may be desirable to modify the antibody of the invention with respect to effector function, so as to enhance, *e.g.*, the effectiveness of the antibody in treating cancer. For example, cysteine residue(s) may be introduced into the Fc region, thereby allowing interchain disulfide bond formation in this region. The homodimeric antibody thus generated may have improved internalization capability and/or increased complement-mediated cell killing and antibody-dependent cellular cytotoxicity (ADCC). *See*, Caron *et al.*, J. Exp. Med., **176**: 1191-1195 (1992) and Shopes, J. Immunol., **148**: 2918-2922 (1992). Homodimeric antibodies with enhanced anti-tumor activity may also be prepared using heterobifunctional cross-linkers as described in Wolff *et al.*, Cancer Research, **53**: 2560-2565 (1993). Alternatively, an antibody can be engineered that has dual Fc regions and may thereby have enhanced complement lysis and ADCC capabilities. *See*, Stevenson *et al.*, Anti-Cancer Drug Design, **3**: 219-230 (1989).

#### 5.2.5.7. Immunoconjugates

The invention also pertains to immunoconjugates comprising an antibody conjugated to a cytotoxic agent such as a chemotherapeutic agent, toxin (*e.g.*, an enzymatically active toxin of bacterial, fungal, plant, or animal origin, or fragments thereof), or a radioactive isotope (*i.e.*, a radioconjugate).

Chemotherapeutic agents useful in the generation of such immunoconjugates have been described above. Enzymatically active toxins and fragments thereof that can be used include diphtheria A chain, nonbinding active fragments of diphtheria toxin, exotoxin A chain (from *Pseudomonas aeruginosa*), ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, *Aleurites fordii* proteins, dianthin proteins, *Phytolacca americana* proteins (PAPI, PAPII, and PAP-S), momordica charantia inhibitor, curcin, crotin, sapaonaria officinalis inhibitor, gelonin, mitogellin, restrictocin, phenomycin, enomycin, and the tricothecenes. A variety of radionuclides are available for the production of radioconjugated antibodies. Examples include  $^{212}\text{Bi}$ ,  $^{131}\text{I}$ ,  $^{131}\text{In}$ ,  $^{90}\text{Y}$ , and  $^{186}\text{Re}$ .

Conjugates of the antibody and cytotoxic agent are made using a variety of bifunctional protein-coupling agents such as N-succinimidyl-3-(2-pyridyldithiol) propionate (SPDP), iminothiolane (IT), bifunctional derivatives

of imidoesters (such as dimethyl adipimidate HCl), active esters (such as disuccinimidyl suberate), aldehydes (such as glutaraldehyde), bis-azido compounds (such as bis (p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as tolyene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene). For example, a ricin immunotoxin can be prepared as described in Vitetta *et al.*, Science, **238**: 1098 (1987). Carbon-14-labeled 1-isothiocyanatobenzyl-3-methyldiethylene triaminepentaacetic acid (MX-DTPA) is an exemplary chelating agent for conjugation of radionucleotide to the antibody. See, WO94/11026.

In another embodiment, the antibody may be conjugated to a "receptor" (such as streptavidin) for utilization in tumor pretargeting wherein the antibody-receptor conjugate is administered to the patient, followed by removal of unbound conjugate from the circulation using a clearing agent and then administration of a "ligand" (e.g., avidin) that is conjugated to a cytotoxic agent (e.g., a radionucleotide).

#### 5.2.5.8. Immunoliposomes

The antibodies disclosed herein may also be formulated as immunoliposomes. Liposomes containing the antibody are prepared by methods known in the art, such as described in Epstein *et al.*, Proc. Natl. Acad. Sci. USA, **82**: 3688 (1985); Hwang *et al.*, Proc. Natl. Acad. Sci. USA, **77**: 4030 (1980); and U.S. Pat. Nos. 4,485,045 and 4,544,545. Liposomes with enhanced circulation time are disclosed in U.S. Patent No. 5,013,556.

Particularly useful liposomes can be generated by the reverse-phase evaporation method with a lipid composition comprising phosphatidylcholine, cholesterol, and PEG-derivatized phosphatidylethanolamine (PEG-PE). Liposomes are extruded through filters of defined pore size to yield liposomes with the desired diameter. Fab' fragments of the antibody of the present invention can be conjugated to the liposomes as described in Martin *et al.*, J. Biol. Chem., **257**: 286-288 (1982) via a disulfide-interchange reaction. A chemotherapeutic agent (such as Doxorubicin) is optionally contained within the liposome. See, Gabizon *et al.*, J. National Cancer Inst., **81**(19): 1484 (1989).

#### 5.2.5.9. Pharmaceutical Compositions of Antibodies

Antibodies specifically binding a PRO polypeptide identified herein, as well as other molecules identified by the screening assays disclosed hereinbefore, can be administered for the treatment of various disorders as noted above and below in the form of pharmaceutical compositions.

If the PRO polypeptide is intracellular and whole antibodies are used as inhibitors, internalizing antibodies are preferred. However, lipofections or liposomes can also be used to deliver the antibody, or an antibody fragment, into cells. Where antibody fragments are used, the smallest inhibitory fragment that specifically binds to the binding domain of the target protein is preferred. For example, based upon the variable-region sequences of an antibody, peptide molecules can be designed that retain the ability to bind the target protein sequence. Such peptides can be synthesized chemically and/or produced by recombinant DNA technology. See, e.g., Marasco *et al.*, Proc. Natl. Acad. Sci. USA, **90**: 7889-7893 (1993).

The formulation herein may also contain more than one active compound as necessary for the particular indication being treated, preferably those with complementary activities that do not adversely affect each other. Alternatively, or in addition, the composition may comprise an agent that enhances its function, such as, for example, a cytotoxic agent, cytokine, chemotherapeutic agent, or growth-inhibitory agent. Such molecules are suitably present in combination in amounts that are effective for the purpose intended.

The active ingredients may also be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacrylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles, and nanocapsules) or in macroemulsions. Such techniques are disclosed in Remington's Pharmaceutical Sciences, *supra*.

The formulations to be used for *in vivo* administration must be sterile. This is readily accomplished by filtration through sterile filtration membranes.

Sustained-release preparations may be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the antibody, which matrices are in the form of shaped articles, *e.g.*, films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinylalcohol)), polylactides (U.S. Pat. No. 3,773,919), copolymers of L-glutamic acid and  $\gamma$  ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT<sup>TM</sup> (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)-3-hydroxybutyric acid. While polymers such as ethylene-vinyl acetate and lactic acid-glycolic acid enable release of molecules for over 100 days, certain hydrogels release proteins for shorter time periods. When encapsulated antibodies remain in the body for a long time, they may denature or aggregate as a result of exposure to moisture at 37°C, resulting in a loss of biological activity and possible changes in immunogenicity. Rational strategies can be devised for stabilization depending on the mechanism involved. For example, if the aggregation mechanism is discovered to be intermolecular S-S bond formation through thio-disulfide interchange, stabilization may be achieved by modifying sulfhydryl residues, lyophilizing from acidic solutions, controlling moisture content, using appropriate additives, and developing specific polymer matrix compositions.

#### 5.2.5.10. Methods of Treatment using the Antibody

It is contemplated that the antibodies to a PRO polypeptide may be used to treat various cardiovascular, endothelial, and angiogenic conditions as noted above.

The antibodies are administered to a mammal, preferably a human, in accord with known methods, such as intravenous administration as a bolus or by continuous infusion over a period of time, by intramuscular, intraperitoneal, intracerebrospinal, subcutaneous, intra-articular, intrasynovial, intrathecal, oral, topical, or inhalation routes. Intravenous administration of the antibody is preferred.

Other therapeutic regimens may be combined with the administration of the antibodies of the instant invention as noted above. For example, if the antibodies are to treat cancer, the patient to be treated with such

antibodies may also receive radiation therapy. Alternatively, or in addition, a chemotherapeutic agent may be administered to the patient. Preparation and dosing schedules for such chemotherapeutic agents may be used according to manufacturers' instructions or as determined empirically by the skilled practitioner. Preparation and dosing schedules for such chemotherapy are also described in Chemotherapy Service, Ed., M.C. Perry (Williams & Wilkins: Baltimore, MD, 1992). The chemotherapeutic agent may precede, or follow administration of the antibody, or may be given simultaneously therewith. The antibody may be combined with an anti-estrogen compound such as tamoxifen or EVISTA™ or an anti-progesterone such as onapristone (*see*, EP 616812) in dosages known for such molecules.

If the antibodies are used for treating cancer, it may be desirable also to administer antibodies against other tumor-associated antigens, such as antibodies that bind to one or more of the ErbB2, EGFR, ErbB3, ErbB4, or VEGF receptor(s). These also include the agents set forth above. Also, the antibody is suitably administered serially or in combination with radiological treatments, whether involving irradiation or administration of radioactive substances. Alternatively, or in addition, two or more antibodies binding the same or two or more different antigens disclosed herein may be co-administered to the patient. Sometimes, it may be beneficial also to administer one or more cytokines to the patient. In a preferred embodiment, the antibodies herein are co-administered with a growth-inhibitory agent. For example, the growth-inhibitory agent may be administered first, followed by an antibody of the present invention. However, simultaneous administration or administration of the antibody of the present invention first is also contemplated. Suitable dosages for the growth-inhibitory agent are those presently used and may be lowered due to the combined action (synergy) of the growth-inhibitory agent and the antibody herein.

In one embodiment, vascularization of tumors is attacked in combination therapy. The anti-PRO polypeptide antibody and another antibody (*e.g.*, anti-VEGF) are administered to tumor-bearing patients at therapeutically effective doses as determined, for example, by observing necrosis of the tumor or its metastatic foci, if any. This therapy is continued until such time as no further beneficial effect is observed or clinical examination shows no trace of the tumor or any metastatic foci. Then TNF is administered, alone or in combination with an auxiliary agent such as alpha-, beta-, or gamma-interferon, anti-HER2 antibody, heregulin, anti-heregulin antibody, D-factor, interleukin-1 (IL-1), interleukin-2 (IL-2), granulocyte-macrophage colony stimulating factor (GM-CSF), or agents that promote microvascular coagulation in tumors, such as anti-protein C antibody, anti-protein S antibody, or C4b binding protein (*see*, WO 91/01753, published 21 February 1991), or heat or radiation.

Since the auxiliary agents will vary in their effectiveness, it is desirable to compare their impact on the tumor by matrix screening in conventional fashion. The administration of anti-PRO polypeptide antibody and TNF is repeated until the desired clinical effect is achieved. Alternatively, the anti-PRO polypeptide antibody is administered together with TNF and, optionally, auxiliary agent(s). In instances where solid tumors are found in the limbs or in other locations susceptible to isolation from the general circulation, the therapeutic agents described herein are administered to the isolated tumor or organ. In other embodiments, a FGF or PDGF antagonist, such as an anti-FGF or an anti-PDGF neutralizing antibody, is administered to the patient in conjunction with the anti-PRO

polypeptide antibody. Treatment with anti-PRO polypeptide antibodies preferably may be suspended during periods of wound healing or desirable neovascularization.

For the prevention or treatment of cardiovascular, endothelial, and angiogenic disorder, the appropriate dosage of an antibody herein will depend on the type of disorder to be treated, as defined above, the severity and course of the disease, whether the antibody is administered for preventive or therapeutic purposes, previous therapy, the patient's clinical history and response to the antibody, and the discretion of the attending physician. The antibody is suitably administered to the patient at one time or over a series of treatments.

For example, depending on the type and severity of the disorder, about 1  $\mu$ g/kg to 50 mg/kg (*e.g.*, 0.1-20 mg/kg) of antibody is an initial candidate dosage for administration to the patient, whether, for example, by one or more separate administrations, or by continuous infusion. A typical daily or weekly dosage might range from about 1  $\mu$ g/kg to 100 mg/kg or more, depending on the factors mentioned above. For repeated administrations over several days or longer, depending on the condition, the treatment is repeated or sustained until a desired suppression of disorder symptoms occurs. However, other dosage regimens may be useful. The progress of this therapy is easily monitored by conventional techniques and assays, including, for example, radiographic tumor imaging.

#### 5.2.5.11. Articles of Manufacture with Antibodies

An article of manufacture containing a container with the antibody and a label is also provided. Such articles are described above, wherein the active agent is an anti-PRO antibody.

#### 5.2.5.12. Diagnosis and Prognosis of Tumors using Antibodies

If the indication for which the antibodies are used is cancer, while cell-surface proteins, such as growth receptors over expressed in certain tumors, are excellent targets for drug candidates or tumor (*e.g.*, cancer) treatment, the same proteins along with PRO polypeptides find additional use in the diagnosis and prognosis of tumors. For example, antibodies directed against the PRO polypeptides may be used as tumor diagnostics or prognostics.

For example, antibodies, including antibody fragments, can be used qualitatively or quantitatively to detect the expression of genes including the gene encoding the PRO polypeptide. The antibody preferably is equipped with a detectable, *e.g.*, fluorescent label, and binding can be monitored by light microscopy, flow cytometry, fluorimetry, or other techniques known in the art. Such binding assays are performed essentially as described above.

*In situ* detection of antibody binding to the marker gene products can be performed, for example, by immunofluorescence or immunoelectron microscopy. For this purpose, a histological specimen is removed from the patient, and a labeled antibody is applied to it, preferably by overlaying the antibody on a biological sample. This procedure also allows for determining the distribution of the marker gene product in the tissue examined. It will be apparent to those skilled in the art that a wide variety of histological methods are readily available for *in situ* detection.

The following Examples are offered for illustrative purposes only, and are not intended to limit the scope of the present invention in any way.

The disclosures of all patent and literature references cited in the present specification are hereby incorporated by reference in their entirety.

5        6.        EXAMPLES

Commercially available reagents referred to in the Examples were used according to manufacturer's instructions unless otherwise indicated. The source of those cells identified in the following Examples, and throughout the specification, by ATCC accession numbers is the American Type Culture Collection, Manassas, VA. Unless otherwise noted, the present invention uses standard procedures of recombinant DNA technology, such as those described hereinabove and in the following textbooks: Sambrook *et al.*, *supra*; Ausubel *et al.*, Current Protocols in Molecular Biology (Green Publishing Associates and Wiley Interscience, N.Y., 1989); Innis *et al.*, PCR Protocols: A Guide to Methods and Applications (Academic Press, Inc.: N.Y., 1990); Harlow *et al.*, Antibodies: A Laboratory Manual (Cold Spring Harbor Press: Cold Spring Harbor, 1988); Gait, Oligonucleotide Synthesis (IRL Press: Oxford, 1984); Freshney, Animal Cell Culture, 1987; Coligan *et al.*, Current Protocols in Immunology, 1991.

15            6.1.        EXAMPLE 1:    Extracellular Domain Homology Screening to Identify Novel Polypeptides and cDNA Encoding Therefor

The extracellular domain (ECD) sequences (including the secretion signal sequence, if any) from about 950 known secreted proteins from the Swiss-Prot public database were used to search EST databases. The EST databases included public databases (*e.g.*, Dayhoff, GenBank), and proprietary databases (*e.g.* LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA). The search was performed using the computer program BLAST or BLAST-2 (Altschul *et al.*, Methods in Enzymology, 266:460-480 (1996)) as a comparison of the ECD protein sequences to a 6 frame translation of the EST sequences. Those comparisons with a BLAST score of 70 (or in some cases, 90) or greater that did not encode known proteins were clustered and assembled into consensus DNA sequences with the program "phrap" (Phil Green, University of Washington, Seattle, WA).

25            Using this extracellular domain homology screen, consensus DNA sequences were assembled relative to the other identified EST sequences using phrap. In addition, the consensus DNA sequences obtained were often (but not always) extended using repeated cycles of BLAST or BLAST-2 and phrap to extend the consensus sequence as far as possible using the sources of EST sequences discussed above.

30            Based upon the consensus sequences obtained as described above, oligonucleotides were then synthesized and used to identify by PCR a cDNA library that contained the sequence of interest and for use as probes to isolate a clone of the full-length coding sequence for a PRO polypeptide. Forward and reverse PCR primers generally range from 20 to 30 nucleotides and are often designed to give a PCR product of about 100-1000 bp in length. The probe sequences are typically 40-55 bp in length. In some cases, additional oligonucleotides are synthesized when the consensus sequence is greater than about 1-1.5 kbp. In order to screen several libraries for a full-length clone, 35        DNA from the libraries was screened by PCR amplification, as per Ausubel *et al.*, Current Protocols in Molecular

Biology, with the PCR primer pair. A positive library was then used to isolate clones encoding the gene of interest using the probe oligonucleotide and one of the primer pairs.

The cDNA libraries used to isolate the cDNA clones were constructed by standard methods using commercially available reagents such as those from Invitrogen, San Diego, CA. The cDNA was primed with oligo dT containing a NotI site, linked with blunt to SalI hemikinased adaptors, cleaved with NotI, sized appropriately by gel electrophoresis, and cloned in a defined orientation into a suitable cloning vector (such as pRKB or pRKD; pRK5B is a precursor of pRK5D that does not contain the SfiI site; *see*, Holmes *et al.*, Science, 253:1278-1280 (1991)) in the unique XhoI and NotI sites.

## 6.2. EXAMPLE 2: Isolation of cDNA Clones by Amylase Screening

### 6.2.1. Preparation of oligo dT primed cDNA library

mRNA was isolated from a human tissue of interest using reagents and protocols from Invitrogen, San Diego, CA (Fast Track 2). This RNA was used to generate an oligo dT primed cDNA library in the vector pRK5D using reagents and protocols from Life Technologies, Gaithersburg, MD (Super Script Plasmid System). In this procedure, the double stranded cDNA was sized to greater than 1000 bp and the SalI/NotI linked cDNA was cloned into XhoI/NotI cleaved vector. pRK5D is a cloning vector that has an sp6 transcription initiation site followed by an SfiI restriction enzyme site preceding the XhoI/NotI cDNA cloning sites.

### 6.2.2. Preparation of random primed cDNA library

A secondary cDNA library was generated in order to preferentially represent the 5' ends of the primary cDNA clones. Sp6 RNA was generated from the primary library (described above), and this RNA was used to generate a random primed cDNA library in the vector pSST-AMY.0 using reagents and protocols from Life Technologies (Super Script Plasmid System, referenced above). In this procedure the double stranded cDNA was sized to 500-1000 bp, linked with blunt to NotI adaptors, cleaved with SfiI, and cloned into SfiI/NotI cleaved vector. pSST-AMY.0 is a cloning vector that has a yeast alcohol dehydrogenase promoter preceding the cDNA cloning sites and the mouse amylase sequence (the mature sequence without the secretion signal) followed by the yeast alcohol dehydrogenase terminator, after the cloning sites. Thus, cDNAs cloned into this vector that are fused in frame with amylase sequence will lead to the secretion of amylase from appropriately transfected yeast colonies.

### 6.2.3. Transformation and Detection

DNA from the library described in paragraph 2 above was chilled on ice to which was added electrocompetent DH10B bacteria (Life Technologies, 20 ml). The bacteria and vector mixture was then electroporated as recommended by the manufacturer. Subsequently, SOC media (Life Technologies, 1 ml) was added and the mixture was incubated at 37°C for 30 minutes. The transformants were then plated onto 20 standard 150 mm LB plates containing ampicillin and incubated for 16 hours (37°C). Positive colonies were scraped off the plates and the DNA was isolated from the bacterial pellet using standard protocols, *e.g.*, CsCl-gradient. The purified DNA was then carried on to the yeast protocols below.

The yeast methods were divided into three categories: (1) Transformation of yeast with the plasmid/cDNA combined vector; (2) Detection and isolation of yeast clones secreting amylase; and (3) PCR amplification of the insert directly from the yeast colony and purification of the DNA for sequencing and further analysis.

5 The yeast strain used was HD56-5A (ATCC-90785). This strain has the following genotype: MAT alpha, ura3-52, leu2-3, leu2-112, his3-11, his3-15, MAL<sup>+</sup>, SUC<sup>+</sup>, GAL<sup>+</sup>. Preferably, yeast mutants can be employed that have deficient post-translational pathways. Such mutants may have translocation deficient alleles in *sec71*, *sec72*, *sec62*, with truncated *sec71* being most preferred. Alternatively, antagonists (including antisense nucleotides and/or ligands) which interfere with the normal operation of these genes, other proteins implicated in this post translation pathway (e.g., SEC61p, SEC72p, SEC62p, SEC63p, TDJ1p or SSA1p-4p) or the complex formation  
10 of these proteins may also be preferably employed in combination with the amylase-expressing yeast.

Transformation was performed based on the protocol outlined by Gietz *et al.*, Nucl. Acid. Res., 20:1425 (1992). Transformed cells were then inoculated from agar into YEPD complex media broth (100 ml) and grown overnight at 30°C. The YEPD broth was prepared as described in Kaiser *et al.*, Methods in Yeast Genetics, Cold Spring Harbor Press, Cold Spring Harbor, NY, p. 207 (1994). The overnight culture was then diluted to about 2  
15 x 10<sup>6</sup> cells/ml (approx. OD<sub>600</sub>=0.1) into fresh YEPD broth (500 ml) and regrown to 1 x 10<sup>7</sup> cells/ml (approx. OD<sub>600</sub>=0.4-0.5).

The cells were then harvested and prepared for transformation by transfer into GS3 rotor bottles in a Sorval GS3 rotor at 5,000 rpm for 5 minutes, the supernatant discarded, and then resuspended into sterile water, and centrifuged again in 50 ml falcon tubes at 3,500 rpm in a Beckman GS-6KR centrifuge. The supernatant was  
20 discarded and the cells were subsequently washed with LiAc/TE (10 ml, 10 mM Tris-HCl, 1 mM EDTA pH 7.5, 100 mM Li<sub>2</sub>OOCCH<sub>3</sub>), and resuspended into LiAc/TE (2.5 ml).

Transformation took place by mixing the prepared cells (100 µl) with freshly denatured single stranded salmon testes DNA (Lofstrand Labs, Gaithersburg, MD) and transforming DNA (1 µg, vol. < 10 µl) in microfuge tubes. The mixture was mixed briefly by vortexing, then 40% PEG/TE (600 µl, 40% polyethylene glycol-4000, 10 mM Tris-HCl, 1 mM EDTA, 100 mM Li<sub>2</sub>OOCCH<sub>3</sub>, pH 7.5) was added. This mixture was gently mixed and  
25 incubated at 30°C while agitating for 30 minutes. The cells were then heat shocked at 42°C for 15 minutes, and the reaction vessel centrifuged in a microfuge at 12,000 rpm for 5-10 seconds, decanted and resuspended into TE (500 µl, 10 mM Tris-HCl, 1 mM EDTA pH 7.5) followed by recentrifugation. The cells were then diluted into TE (1 ml) and aliquots (200 µl) were spread onto the selective media previously prepared in 150 mm growth plates (VWR).  
30

Alternatively, instead of multiple small reactions, the transformation was performed using a single, large scale reaction, wherein reagent amounts were scaled up accordingly.

The selective media used was a synthetic complete dextrose agar lacking uracil (SCD-Ura) prepared as described in Kaiser *et al.*, Methods in Yeast Genetics, Cold Spring Harbor Press, Cold Spring Harbor, NY, p. 208-  
35 210 (1994). Transformants were grown at 30°C for 2-3 days.

The detection of colonies secreting amylase was performed by including red starch in the selective growth media. Starch was coupled to the red dye (Reactive Red-120, Sigma) as per the procedure described by Biely *et*



*al.*, Anal. Biochem., 172:176-179 (1988). The coupled starch was incorporated into the SCD-Ura agar plates at a final concentration of 0.15% (w/v), and was buffered with potassium phosphate to a pH of 7.0 (50-100 mM final concentration).

The positive colonies were picked and streaked across fresh selective media (onto 150 mm plates) in order to obtain well isolated and identifiable single colonies. Well isolated single colonies positive for amylase secretion were detected by direct incorporation of red starch into buffered SCD-Ura agar. Positive colonies were determined by their ability to break down starch resulting in a clear halo around the positive colony visualized directly.

#### 6.2.4. Isolation of DNA by PCR Amplification

When a positive colony was isolated, a portion of it was picked by a toothpick and diluted into sterile water (30 µl) in a 96 well plate. At this time, the positive colonies were either frozen and stored for subsequent analysis or immediately amplified. An aliquot of cells (5 µl) was used as a template for the PCR reaction in a 25 µl volume containing: 0.5 µl KlenTaq (Clontech, Palo Alto, CA); 4.0 µl 10 mM dNTP's (Perkin Elmer-Cetus); 2.5 µl KlenTaq buffer (Clontech); 0.25 µl forward oligo 1; 0.25 µl reverse oligo 2; 12.5 µl distilled water. The sequence of the forward oligonucleotide 1 was:

5'-TGTAACGACGCGCCAGTTAAATAGACCTGCAATTATTAATCT-3' (SEQ ID NO:382)

The sequence of reverse oligonucleotide 2 was:

5'-CAGGAAACAGCTATGACCACCTGCACACCTGCAAATCCATT-3' (SEQ ID NO:383)

PCR was then performed as follows:

|    |               |                  |
|----|---------------|------------------|
| a. | Denature      | 92°C, 5 minutes  |
| b. | 3 cycles of:  |                  |
|    | Denature      | 92°C, 30 seconds |
|    | Anneal        | 59°C, 30 seconds |
|    | Extend        | 72°C, 60 seconds |
| c. | 3 cycles of:  |                  |
|    | Denature      | 92°C, 30 seconds |
|    | Anneal        | 57°C, 30 seconds |
|    | Extend        | 72°C, 60 seconds |
| d. | 25 cycles of: |                  |
|    | Denature      | 92°C, 30 seconds |
|    | Anneal        | 55°C, 30 seconds |
|    | Extend        | 72°C, 60 seconds |
| e. | Hold          | 4°C              |

The underlined regions of the oligonucleotides annealed to the ADH promoter region and the amylase region, respectively, and amplified a 307 bp region from vector pSST-AMY.0 when no insert was present. Typically, the first 18 nucleotides of the 5' end of these oligonucleotides contained annealing sites for the sequencing primers. Thus, the total product of the PCR reaction from an empty vector was 343 bp. However, signal sequence-fused cDNA resulted in considerably longer nucleotide sequences.

Following the PCR, an aliquot of the reaction (5 µl) was examined by agarose gel electrophoresis in a 1% agarose gel using a Tris-Borate-EDTA (TBE) buffering system as described by Sambrook *et al.*, *supra*. Clones resulting in a single strong PCR product larger than 400 bp were further analyzed by DNA sequencing after purification with a 96 Qiaquick PCR clean-up column (Qiagen Inc., Chatsworth, CA).

5           6.3.    EXAMPLE 3: Isolation of cDNA Clones Using Signal Algorithm Analysis

Various polypeptide-encoding nucleic acid sequences were identified by applying a proprietary signal sequence finding algorithm developed by Genentech, Inc., (South San Francisco, CA) upon ESTs as well as clustered and assembled EST fragments from public (e.g., GenBank) and/or private (LIFESEQ®, Incyte Pharmaceuticals, Inc., Palo Alto, CA) databases. The signal sequence algorithm computes a secretion signal score based on the character of the DNA nucleotides surrounding the first and optionally the second methionine codon(s) (ATG) at the 5'-end of the sequence or sequence fragment under consideration. The nucleotides following the first ATG must code for at least 35 unambiguous amino acids without any stop codons. If the first ATG has the required amino acids, the second is not examined. If neither meets the requirement, the candidate sequence is not scored. In order to determine whether the EST sequence contains an authentic signal sequence, the DNA and corresponding amino acid sequences surrounding the ATG codon are scored using a set of seven sensors (evaluation parameters) known to be associated with secretion signals. Use of this algorithm resulted in the identification of numerous polypeptide-encoding nucleic acid sequences.

          6.4.    EXAMPLE 4: Isolation of cDNA clones Encoding Human PRO Polypeptides

Using the techniques described in Examples 1 to 3 above, numerous full-length cDNA clones were identified as encoding PRO polypeptides as disclosed herein. These cDNAs were then deposited under the terms of the Budapest Treaty with the American Type Culture Collection, 10801 University Blvd., Manassas, VA 20110-2209, USA (ATCC) as shown in Table 7 below.

Table 7

| <u>Material</u> | <u>ATCC Dep. No.</u> | <u>Deposit Date</u> |
|-----------------|----------------------|---------------------|
| 23330-1390      | 209775               | 4/14/1998           |
| 23339-1130      | 209282               | 9/18/1997           |
| 26846-1397      | 203406               | 10/27/1998          |
| 26847-1395      | 209772               | 4/14/1998           |
| 27865-1091      | 209296               | 9/23/1997           |
| 30868-1156      | 1437-PTA             | 3/2/2000            |
| 30871-1157      | 209380               | 10/16/1997          |
| 32286-1191      | 209385               | 10/16/1997          |
| 33089-1132      | 209262               | 9/16/1997           |
| 33092-1202      | 209420               | 10/28/1997          |

|    |              |        |            |
|----|--------------|--------|------------|
|    | 33100-1159   | 209377 | 10/16/1997 |
|    | 33223-1136   | 209264 | 9/16/1997  |
|    | 34392-1170   | 209526 | 12/10/1997 |
|    | 34431-1177   | 209399 | 10/17/1997 |
| 5  | 34433-1308   | 209719 | 3/31/1998  |
|    | 34434-1139   | 209252 | 9/16/1997  |
|    | 35600-1162   | 209370 | 10/16/1997 |
|    | 35673-1201   | 209418 | 10/28/1997 |
|    | 35880-1160   | 209379 | 10/16/1997 |
| 10 | 35918-1174   | 209402 | 10/17/1997 |
|    | 36350-1158   | 209378 | 10/16/1997 |
|    | 36638-1056   | 209456 | 11/12/1997 |
|    | 38268-1188   | 209421 | 10/28/1997 |
|    | 40370-1217   | 209485 | 11/21/1997 |
| 15 | 40628-1216   | 209432 | 11/7/1997  |
|    | 43316-1237   | 209487 | 11/21/1997 |
|    | 44196-1353   | 209847 | 5/6/1998   |
|    | 45409-2511   | 203579 | 1/12/1999  |
|    | 45419-1252   | 209616 | 2/5/1998   |
| 20 | 46777-1253   | 209619 | 2/5/1998   |
|    | 48336-1309   | 209669 | 3/11/1998  |
|    | 48606-1479   | 203040 | 7/1/1998   |
|    | 49435-1219   | 209480 | 11/21/1997 |
|    | 49631-1328   | 209806 | 4/28/1998  |
| 25 | 50919-1361   | 209848 | 5/6/1998   |
|    | 50920-1325   | 209700 | 3/26/1998  |
|    | 50921-1458   | 209859 | 5/12/1998  |
|    | 52758-1399   | 209773 | 4/14/1998  |
|    | 53517-1366-1 | 209802 | 4/23/1998  |
| 30 | 53915-1258   | 209593 | 1/21/1998  |
|    | 53974-1401   | 209774 | 4/14/1998  |
|    | 53987-1438   | 209858 | 5/12/1998  |
|    | 56047-1456   | 209948 | 6/9/1998   |
|    | 56050-1455   | 203011 | 6/23/1998  |
| 35 | 56110-1437   | 203113 | 8/11/1998  |
|    | 56405-1357   | 209849 | 5/6/1998   |
|    | 56433-1406   | 209857 | 5/12/1998  |

|    |              |        |            |
|----|--------------|--------|------------|
|    | 56439-1376   | 209864 | 5/14/1998  |
|    | 56529-1647   | 203293 | 9/29/1998  |
|    | 56865-1491   | 203022 | 6/23/1998  |
|    | 56965-1356   | 209842 | 5/6/1998   |
| 5  | 57033-1403-1 | 209905 | 5/27/1998  |
|    | 57037-1444   | 209903 | 5/27/1998  |
|    | 57039-1402   | 209777 | 4/14/1998  |
|    | 57689-1385   | 209869 | 5/14/1998  |
|    | 57690-1374   | 209950 | 6/9/1998   |
| 10 | 57694-1341   | 203017 | 6/23/1998  |
|    | 57695-1340   | 203006 | 6/23/1998  |
|    | 57699-1412   | 203020 | 6/23/1998  |
|    | 57700-1408   | 203583 | 1/12/1999  |
|    | 57708-1411   | 203021 | 6/23/1998  |
| 15 | 57838-1337   | 203014 | 6/23/1998  |
|    | 58847-1383   | 209879 | 5/20/1998  |
|    | 58852-1637   | 203271 | 9/22/1998  |
|    | 58853-1423   | 203016 | 6/23/1998  |
|    | 59212-1627   | 203245 | 9/9/1998   |
| 20 | 59220-1514   | 209962 | 6/9/1998   |
|    | 59493-1420   | 203050 | 7/1/1998   |
|    | 59497-1496   | 209941 | 6/4/1998   |
|    | 59586-1520   | 203288 | 9/29/1998  |
|    | 59588-1571   | 203106 | 8/11/1998  |
| 25 | 59620-1463   | 209989 | 6/16/1998  |
|    | 59622-1334   | 209984 | 6/16/1998  |
|    | 59777-1480   | 203111 | 8/11/1998  |
|    | 59848-1512   | 203088 | 8/4/1998   |
|    | 59849-1504   | 209986 | 6/16/1998  |
| 30 | 60621-1516   | 203091 | 8/4/1998   |
|    | 60622-1525   | 203090 | 8/4/1998   |
|    | 60764-1533   | 203452 | 11/10/1998 |
|    | 60783-1611   | 203130 | 8/18/1998  |
|    | 61755-1554   | 203112 | 8/11/1998  |
| 35 | 62306-1570   | 203254 | 9/9/1998   |
|    | 62312-2558   | 203836 | 3/9/1999   |
|    | 62814-1521   | 203093 | 8/4/1998   |

|    |              |         |            |
|----|--------------|---------|------------|
|    | 62872-1509   | 203100  | 8/4/1998   |
|    | 64883-1526   | 203253  | 9/9/1998   |
|    | 64886-1601   | 203241  | 9/9/1998   |
|    | 64889-1541   | 203250  | 9/9/1998   |
| 5  | 64896-1539   | 203238  | 9/9/1998   |
|    | 64897-1628   | 203216  | 9/15/1998  |
|    | 64903-1553   | 203223  | 9/15/1998  |
|    | 64908-1163-1 | 203243  | 9/9/1998   |
|    | 64950-1590   | 203224  | 9/15/1998  |
| 10 | 65402-1540   | 203252  | 9/9/1998   |
|    | 65404-1551   | 203244  | 9/9/1998   |
|    | 65405-1547   | 203476  | 11/17/1998 |
|    | 65410-1569   | 203231  | 9/15/1998  |
|    | 65412-1523   | 203094  | 8/4/1998   |
| 15 | 66307-2661   | 431-PTA | 7/27/1999  |
|    | 66526-1616   | 203246  | 9/9/1998   |
|    | 66659-1593   | 203269  | 9/22/1998  |
|    | 66660-1585   | 203279  | 9/22/1998  |
|    | 66667-1596   | 203267  | 9/22/1998  |
| 20 | 66672-1586   | 203265  | 9/22/1998  |
|    | 66675-1587   | 203282  | 9/22/1998  |
|    | 67300-1605   | 203163  | 8/25/1998  |
|    | 68818-2536   | 203657  | 2/9/1999   |
|    | 68862-2546   | 203652  | 2/9/1999   |
| 25 | 68872-1620   | 203160  | 8/25/1998  |
|    | 71290-1630   | 203275  | 9/22/1998  |
|    | 73736-1657   | 203466  | 11/17/1998 |
|    | 73739-1645   | 203270  | 9/22/1998  |
|    | 73742-1662   | 203316  | 10/6/1998  |
| 30 | 76385-1692   | 203664  | 2/9/1999   |
|    | 76393-1664   | 203323  | 10/6/1998  |
|    | 76399-1700   | 203472  | 11/17/1998 |
|    | 76400-2528   | 203573  | 1/12/1999  |
|    | 76510-2504   | 203477  | 11/17/1998 |
| 35 | 76529-1666   | 203315  | 10/6/1998  |
|    | 76532-1702   | 203473  | 11/17/1998 |
|    | 76541-1675   | 203409  | 10/27/1998 |

|    |              |          |            |
|----|--------------|----------|------------|
|    | 77503-1686   | 203362   | 10/20/1998 |
|    | 77624-2515   | 203553   | 12/22/1998 |
|    | 79230-2525   | 203549   | 12/22/1998 |
|    | 79862-2522   | 203550   | 12/22/1998 |
| 5  | 80145-2594   | 204-PTA  | 6/8/1999   |
|    | 80899-2501   | 203539   | 12/15/1998 |
|    | 81754-2532   | 203542   | 12/15/1998 |
|    | 81757-2512   | 203543   | 12/15/1998 |
|    | 81761-2583   | 203862   | 3/23/1999  |
| 10 | 82358-2738   | 510-PTA  | 8/10/1999  |
|    | 82364-2538   | 203603   | 1/20/1999  |
|    | 82403-2959   | 2317-PTA | 8/1/2000   |
|    | 83500-2506   | 203391   | 10/29/1998 |
|    | 83560-2569   | 203816   | 3/2/1999   |
| 15 | 84210-2576   | 203818   | 3/2/1999   |
|    | 84920-2614   | 203966   | 4/27/1999  |
|    | 86576-2595   | 203868   | 3/23/1999  |
|    | 92218-2554   | 203834   | 3/9/1999   |
|    | 92233-2599   | 134-PTA  | 5/25/1999  |
| 20 | 92256-2596   | 203891   | 3/30/1999  |
|    | 92265-2669   | 256-PTA  | 6/22/1999  |
|    | 92274-2617   | 203971   | 4/27/1999  |
|    | 92929-2534-1 | 203586   | 1/12/1999  |
|    | 93011-2637   | 20-PTA   | 5/4/1999   |
| 25 | 94854-2586   | 203864   | 3/23/1999  |
|    | 96787-2534-1 | 203589   | 1/12/1999  |
|    | 96867-2620   | 203972   | 4/27/1999  |
|    | 96872-2674   | 550-PTA  | 8/17/1999  |
|    | 96878-2626   | 23-PTA   | 5/4/1999   |
| 30 | 96889-2641   | 119-PTA  | 5/25/1999  |
|    | 100312-2645  | 44-PTA   | 5/11/1999  |
|    | 105782-2693  | 387-PTA  | 7/20/1999  |
|    | 105849-2704  | 473-PTA  | 8/3/1999   |
|    | 108725-2766  | 863-PTA  | 10/19/1999 |
| 35 | 108769-2765  | 861-PTA  | 10/19/1999 |
|    | 119498-2965  | 2298-PTA | 7/25/2000  |
|    | 119535-2756  | 613-PTA  | 8/31/1999  |

|    |             |          |            |
|----|-------------|----------|------------|
|    | 125185-2806 | 1031-PTA | 12/7/1999  |
|    | 131639-2874 | 1784-PTA | 4/25/2000  |
|    | 139623-2893 | 1670-PTA | 4/11/2000  |
|    | 143076-2787 | 1028-PTA | 12/7/1999  |
| 5  | 143276-2975 | 2387-PTA | 8/8/2000   |
|    | 164625-2890 | 1535-PTA | 3/21/2000  |
|    | 167678-2963 | 2302-PTA | 7/25/2000  |
|    | 170021-2923 | 1906-PTA | 5/23/2000  |
|    | 170212-3000 | 2583-PTA | 10/10/2000 |
| 10 | 177313-2982 | 2251-PTA | 7/19/2000  |

These deposits were made under the provisions of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure and the Regulations thereunder (Budapest Treaty). This assures maintenance of a viable culture of the deposit for 30 years from the date of deposit. The deposits will be made available by ATCC under the terms of the Budapest Treaty, and subject to an agreement between Genentech, Inc. and ATCC, which assures permanent and unrestricted availability of the progeny of the culture of the deposit to the public upon issuance of the pertinent U.S. patent or upon laying open to the public of any U.S. or foreign patent application, whichever comes first, and assures availability of the progeny to one determined by the U.S. Commissioner of Patents and Trademarks to be entitled thereto according to 35 USC § 122 and the Commissioner's rules pursuant thereto (including 37 CFR § 1.14 with particular reference to 886 OG 638).

The assignee of the present application has agreed that if a culture of the materials on deposit should die or be lost or destroyed when cultivated under suitable conditions, the materials will be promptly replaced on notification with another of the same. Availability of the deposited material is not to be construed as a license to practice the invention in contravention of the rights granted under the authority of any government in accordance with its patent laws.

**6.5 EXAMPLE 5: Isolation of cDNA clones Encoding Human PRO1873, PRO7223, PRO7248, PRO730, PRO532, PRO7261, PRO734, PRO771, PRO2010, PRO5723, PRO3444, PRO9940, PRO3562, PRO10008, PRO5730, PRO6008, PRO4527, PRO4538 and PRO4553**

DNA molecules encoding the PRO1873, PRO7223, PRO7248, PRO730, PRO532, PRO7261, PRO734, PRO771, PRO2010, PRO5723, PRO3444, PRO9940, PRO3562, PRO10008, PRO5730, PRO6008, PRO4527, PRO4538 and PRO4553 polypeptides shown in the accompanying figures were obtained through GenBank.

**6.6. EXAMPLE 6: Use of PRO as a Hybridization Probe**

The following method describes use of a nucleotide sequence encoding PRO as a hybridization probe.

DNA comprising the coding sequence of full-length or mature PRO (as shown in accompanying figures) or a fragment thereof is employed as a probe to screen for homologous DNAs (such as those encoding naturally-occurring variants of PRO) in human tissue cDNA libraries or human tissue genomic libraries.

Hybridization and washing of filters containing either library DNAs is performed under the following high-stringency conditions. Hybridization of radiolabeled probe derived from the gene encoding PRO polypeptide to the filters is performed in a solution of 50% formamide, 5x SSC, 0.1% SDS, 0.1% sodium pyrophosphate, 50 mM sodium phosphate, pH 6.8, 2x Denhardt's solution, and 10% dextran sulfate at 42°C for 20 hours. Washing of the filters is performed in an aqueous solution of 0.1x SSC and 0.1% SDS at 42°C.

DNAs having a desired sequence identity with the DNA encoding full-length native sequence can then be identified using standard techniques known in the art.

#### 6.7. EXAMPLE 7: Expression of PRO in *E. coli*

This example illustrates preparation of an unglycosylated form of PRO by recombinant expression in *E. coli*.

The DNA sequence encoding PRO is initially amplified using selected PCR primers. The primers should contain restriction enzyme sites which correspond to the restriction enzyme sites on the selected expression vector. A variety of expression vectors may be employed. An example of a suitable vector is pBR322 (derived from *E. coli*; see, Bolivar *et al.*, Gene, 2:95 (1977)) which contains genes for ampicillin and tetracycline resistance. The vector is digested with restriction enzyme and dephosphorylated. The PCR amplified sequences are then ligated into the vector. The vector will preferably include sequences which encode for an antibiotic resistance gene, a trp promoter, a poly-His leader (including the first six STII codons, poly-His sequence, and enterokinase cleavage site), the PRO coding region, lambda transcriptional terminator, and an argU gene.

The ligation mixture is then used to transform a selected *E. coli* strain using the methods described in Sambrook *et al.*, *supra*. Transformants are identified by their ability to grow on LB plates and antibiotic resistant colonies are then selected. Plasmid DNA can be isolated and confirmed by restriction analysis and DNA sequencing.

Selected clones can be grown overnight in liquid culture medium such as LB broth supplemented with antibiotics. The overnight culture may subsequently be used to inoculate a larger scale culture. The cells are then grown to a desired optical density, during which the expression promoter is turned on.

After culturing the cells for several more hours, the cells can be harvested by centrifugation. The cell pellet obtained by the centrifugation can be solubilized using various agents known in the art, and the solubilized PRO protein can then be purified using a metal chelating column under conditions that allow tight binding of the protein.

PRO may be expressed in *E. coli* in a poly-His tagged form, using the following procedure. The DNA encoding PRO is initially amplified using selected PCR primers. The primers will contain restriction enzyme sites which correspond to the restriction enzyme sites on the selected expression vector, and other useful sequences providing for efficient and reliable translation initiation, rapid purification on a metal chelation column, and proteolytic removal with enterokinase. The PCR-amplified, poly-His tagged sequences are then ligated into an



expression vector, which is used to transform an *E. coli* host based on strain 52 (W3110 *fnhA(tonA) lon galE rpoHts(htpRts) clpP(lacIq)*). Transformants are first grown in LB containing 50 mg/ml carbenicillin at 30°C with shaking until an OD<sub>600</sub> of 3-5 is reached. Cultures are then diluted 50-100 fold into CRAP media (prepared by mixing 3.57 g (NH<sub>4</sub>)<sub>2</sub>SO<sub>4</sub>, 0.71 g sodium citrate•2H<sub>2</sub>O, 1.07 g KCl, 5.36 g Difco yeast extract, 5.36 g Sheffield hycase SF in 500 ml water, as well as 110 mM MPOS, pH 7.3, 0.55% (w/v) glucose and 7 mM MgSO<sub>4</sub>) and grown for approximately 20-30 hours at 30°C with shaking. Samples are removed to verify expression by SDS-PAGE analysis, and the bulk culture is centrifuged to pellet the cells. Cell pellets are frozen until purification and refolding.

*E. coli* paste from 0.5 to 1 L fermentations (6-10 g pellets) is resuspended in 10 volumes (w/v) in 7 M guanidine, 20 mM Tris, pH 8 buffer. Solid sodium sulfite and sodium tetrathionate is added to make final concentrations of 0.1M and 0.02 M, respectively, and the solution is stirred overnight at 4°C. This step results in a denatured protein with all cysteine residues blocked by sulfitolization. The solution is centrifuged at 40,000 rpm in a Beckman Ultracentrifuge for 30 min. The supernatant is diluted with 3-5 volumes of metal chelate column buffer (6 M guanidine, 20 mM Tris, pH 7.4) and filtered through 0.22 micron filters to clarify. The clarified extract is loaded onto a 5 ml Qiagen Ni<sup>2+</sup>-NTA metal chelate column equilibrated in the metal chelate column buffer. The column is washed with additional buffer containing 50 mM imidazole (Calbiochem, Utrol grade), pH 7.4. The protein is eluted with buffer containing 250 mM imidazole. Fractions containing the desired protein are pooled and stored at 4°C. Protein concentration is estimated by its absorbance at 280 nm using the calculated extinction coefficient based on its amino acid sequence.

The proteins are refolded by diluting the sample slowly into freshly prepared refolding buffer consisting of: 20 mM Tris, pH 8.6, 0.3 M NaCl, 2.5 M urea, 5 mM cysteine, 20 mM glycine and 1 mM EDTA. Refolding volumes are chosen so that the final protein concentration is between 50 to 100 micrograms/ml. The refolding solution is stirred gently at 4°C for 12-36 hours. The refolding reaction is quenched by the addition of TFA to a final concentration of 0.4% (pH of approximately 3). Before further purification of the protein, the solution is filtered through a 0.22 micron filter and acetonitrile is added to 2-10% final concentration. The refolded protein is chromatographed on a Poros R1/H reversed phase column using a mobile buffer of 0.1% TFA with elution with a gradient of acetonitrile from 10 to 80%. Aliquots of fractions with A<sub>280</sub> absorbance are analyzed on SDS polyacrylamide gels and fractions containing homogeneous refolded protein are pooled. Generally, the properly refolded species of most proteins are eluted at the lowest concentrations of acetonitrile since those species are the most compact with their hydrophobic interiors shielded from interaction with the reversed phase resin. Aggregated species are usually eluted at higher acetonitrile concentrations. In addition to resolving misfolded forms of proteins from the desired form, the reversed phase step also removes endotoxin from the samples.

Fractions containing the desired folded PRO polypeptide are pooled and the acetonitrile removed using a gentle stream of nitrogen directed at the solution. Proteins are formulated into 20 mM Hepes, pH 6.8 with 0.14 M sodium chloride and 4% mannitol by dialysis or by gel filtration using G25 Superfine (Pharmacia) resins equilibrated in the formulation buffer and sterile filtered.

Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

6.8. EXAMPLE 8: Expression of PRO in mammalian cells

This example illustrates preparation of a potentially glycosylated form of PRO by recombinant expression in mammalian cells.

The vector, pRK5 (see EP 307,247, published March 15, 1989), is employed as the expression vector. Optionally, the PRO DNA is ligated into pRK5 with selected restriction enzymes to allow insertion of the PRO DNA using ligation methods such as described in Sambrook *et al.*, *supra*. The resulting vector is called pRK5-PRO.

In one embodiment, the selected host cells may be 293 cells. Human 293 cells (ATCC CCL 1573) are grown to confluence in tissue culture plates in medium such as DMEM supplemented with fetal calf serum and optionally, nutrient components and/or antibiotics. About 10 µg pRK5-PRO DNA is mixed with about 1 µg DNA encoding the VA RNA gene [Thimmappaya *et al.*, *Cell*, 31:543 (1982)] and dissolved in 500 µl of 1 mM Tris-HCl, 0.1 mM EDTA, 0.227 M CaCl<sub>2</sub>. To this mixture is added, dropwise, 500 µl of 50 mM HEPES (pH 7.35), 280 mM NaCl, 1.5 mM NaPO<sub>4</sub>, and a precipitate is allowed to form for 10 minutes at 25°C. The precipitate is suspended and added to the 293 cells and allowed to settle for about four hours at 37°C. The culture medium is aspirated off and 2 ml of 20% glycerol in PBS is added for 30 seconds. The 293 cells are then washed with serum free medium, fresh medium is added and the cells are incubated for about 5 days.

Approximately 24 hours after the transfections, the culture medium is removed and replaced with culture medium (alone) or culture medium containing 200 µCi/ml <sup>35</sup>S-cysteine and 200 µCi/ml <sup>35</sup>S-methionine. After a 12 hour incubation, the conditioned medium is collected, concentrated on a spin filter, and loaded onto a 15% SDS gel. The processed gel may be dried and exposed to film for a selected period of time to reveal the presence of the PRO polypeptide. The cultures containing transfected cells may undergo further incubation (in serum free medium) and the medium is tested in selected bioassays.

In an alternative technique, PRO may be introduced into 293 cells transiently using the dextran sulfate method described by Sompanyrac *et al.*, *Proc. Natl. Acad. Sci.*, 12:7575 (1981). 293 cells are grown to maximal density in a spinner flask and 700 µg pRK5-PRO DNA is added. The cells are first concentrated from the spinner flask by centrifugation and washed with PBS. The DNA-dextran precipitate is incubated on the cell pellet for four hours. The cells are treated with 20% glycerol for 90 seconds, washed with tissue culture medium, and re-introduced into the spinner flask containing tissue culture medium, 5 µg/ml bovine insulin and 0.1 µg/ml bovine transferrin. After about four days, the conditioned media is centrifuged and filtered to remove cells and debris. The sample containing expressed PRO can then be concentrated and purified by any selected method, such as dialysis and/or column chromatography.

In another embodiment, PRO can be expressed in CHO cells. The pRK5-PRO can be transfected into CHO cells using known reagents such as CaPO<sub>4</sub> or DEAE-dextran. As described above, the cell cultures can be incubated, and the medium replaced with culture medium (alone) or medium containing a radiolabel such as <sup>35</sup>S-methionine. After determining the presence of a PRO polypeptide, the culture medium may be replaced with serum free medium. Preferably, the cultures are incubated for about 6 days, and then the conditioned medium is harvested.

The medium containing the expressed PRO polypeptide can then be concentrated and purified by any selected method.

Epitope-tagged PRO may also be expressed in host CHO cells. The PRO may be subcloned out of the pRK5 vector. The subclone insert can undergo PCR to fuse in frame with a selected epitope tag such as a poly-His tag into a Baculovirus expression vector. The poly-His tagged PRO insert can then be subcloned into a SV40 driven vector containing a selection marker such as DHFR for selection of stable clones. Finally, the CHO cells can be transfected (as described above) with the SV40 driven vector. Labeling may be performed, as described above, to verify expression. The culture medium containing the expressed poly-His tagged PRO can then be concentrated and purified by any selected method, such as by Ni<sup>2+</sup>-chelate affinity chromatography.

PRO may also be expressed in CHO and/or COS cells by a transient expression procedure or in CHO cells by another stable expression procedure.

Stable expression in CHO cells is performed using the following procedure. The proteins are expressed as an IgG construct (immunoadhesin), in which the coding sequences for the soluble forms (*e.g.*, extracellular domains) of the respective proteins are fused to an IgG1 constant region sequence containing the hinge, CH2 and CH2 domains and/or as a poly-His tagged form.

Following PCR amplification, the respective DNAs are subcloned in a CHO expression vector using standard techniques as described in Ausubel *et al.*, Current Protocols of Molecular Biology, Unit 3.16, John Wiley and Sons (1997). CHO expression vectors are constructed to have compatible restriction sites 5' and 3' of the DNA of interest to allow the convenient shuttling of cDNA's. The vector used in expression in CHO cells is as described in Lucas *et al.*, Nucl. Acids Res., 24:9 (1774-1779) (1996), and uses the SV40 early promoter/enhancer to drive expression of the cDNA of interest and dihydrofolate reductase (DHFR). DHFR expression permits selection for stable maintenance of the plasmid following transfection.

Twelve micrograms of the desired plasmid DNA is introduced into approximately 10 million CHO cells using commercially available transfection reagents Superfect® (Qiagen), Dospert® or Fugene® (Boehringer Mannheim). The cells are grown as described in Lucas *et al.*, *supra*. Approximately 3 x 10<sup>7</sup> cells are frozen in an ampule for further growth and production as described below.

The ampules containing the plasmid DNA are thawed by placement into a water bath and mixed by vortexing. The contents are pipetted into a centrifuge tube containing 10 ml of media and centrifuged at 1000 rpm for 5 minutes. The supernatant is aspirated and the cells are resuspended in 10 ml of selective media (0.2 µm filtered PS20 with 5% 0.2 µm diafiltered fetal bovine serum). The cells are then aliquoted into a 100 ml spinner containing 90 ml of selective media. After 1-2 days, the cells are transferred into a 250 ml spinner filled with 150 ml selective growth medium and incubated at 37°C. After another 2-3 days, 250 ml, 500 ml and 2000 ml spinners are seeded with 3 x 10<sup>5</sup> cells/ml. The cell media is exchanged with fresh media by centrifugation and resuspension in production medium. Although any suitable CHO media may be employed, a production medium described in U.S. Patent No. 5,122,469, issued June 16, 1992 may actually be used. A 3L production spinner is seeded at 1.2 x 10<sup>6</sup> cells/ml. On day 0, the cell number and pH is determined. On day 1, the spinner is sampled and sparging with filtered air is commenced. On day 2, the spinner is sampled, the temperature shifted to 33°C, and 30 ml of 500 g/L

glucose and 0.6 ml of 10% antifoam (e.g., 35% polydimethylsiloxane emulsion, Dow Corning 365 Medical Grade Emulsion) taken. Throughout the production, the pH is adjusted as necessary to keep it at around 7.2. After 10 days, or until the viability drops below 70%, the cell culture is harvested by centrifugation and filtering through a 0.22  $\mu$ m filter. The filtrate is either stored at 4°C or immediately loaded onto columns for purification.

5 For the poly-His tagged constructs, the proteins are purified using a Ni<sup>2+</sup>-NTA column (Qiagen). Before purification, imidazole is added to the conditioned media to a concentration of 5 mM. The conditioned media is pumped onto a 6 ml Ni<sup>2+</sup>-NTA column equilibrated in 20 mM Hepes, pH 7.4, buffer containing 0.3 M NaCl and 5 mM imidazole at a flow rate of 4-5 ml/min. at 4°C. After loading, the column is washed with additional equilibration buffer and the protein eluted with equilibration buffer containing 0.25 M imidazole. The highly  
10 purified protein is subsequently desalted into a storage buffer containing 10 mM Hepes, 0.14 M NaCl and 4% mannitol, pH 6.8, with a 25 ml G25 Superfine (Pharmacia) column and stored at -80°C.

Immunoadhesin (Fc-containing) constructs are purified from the conditioned media as follows. The conditioned medium is pumped onto a 5 ml Protein A column (Pharmacia) which has been equilibrated in 20 mM Na phosphate buffer, pH 6.8. After loading, the column is washed extensively with equilibration buffer before  
15 elution with 100 mM citric acid, pH 3.5. The eluted protein is immediately neutralized by collecting 1 ml fractions into tubes containing 275  $\mu$ l of 1 M Tris buffer, pH 9. The highly purified protein is subsequently desalted into storage buffer as described above for the poly-His tagged proteins. The homogeneity is assessed by SDS polyacrylamide gels and by N-terminal amino acid sequencing by Edman degradation.

Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

#### 20 6.9. EXAMPLE 9: Expression of PRO in Yeast

The following method describes recombinant expression of PRO in yeast.

First, yeast expression vectors are constructed for intracellular production or secretion of PRO from the ADH2/GAPDH promoter. DNA encoding PRO and the promoter is inserted into suitable restriction enzyme sites in the selected plasmid to direct intracellular expression of PRO. For secretion, DNA encoding PRO can be cloned  
25 into the selected plasmid, together with DNA encoding the ADH2/GAPDH promoter, a native PRO signal peptide or other mammalian signal peptide, or, for example, a yeast alpha-factor or invertase secretory signal/leader sequence, and linker sequences (if needed) for expression of PRO.

Yeast cells, such as yeast strain AB110, can then be transformed with the expression plasmids described above and cultured in selected fermentation media. The transformed yeast supernatants can be analyzed by  
30 precipitation with 10% trichloroacetic acid and separation by SDS-PAGE, followed by staining of the gels with Coomassie Blue stain.

Recombinant PRO can subsequently be isolated and purified by removing the yeast cells from the fermentation medium by centrifugation and then concentrating the medium using selected cartridge filters. The concentrate containing PRO may further be purified using selected column chromatography resins.

35 Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

6.10. EXAMPLE 10: Expression of PRO in Baculovirus-Infected Insect Cells

The following method describes recombinant expression in Baculovirus-infected insect cells.

The sequence coding for PRO is fused upstream of an epitope tag contained within a baculovirus expression vector. Such epitope tags include poly-His tags and immunoglobulin tags (like Fc regions of IgG). A variety of plasmids may be employed, including plasmids derived from commercially available plasmids such as pVL1393 (Novagen). Briefly, the sequence encoding PRO or the desired portion of the coding sequence of PRO (such as the sequence encoding the extracellular domain of a transmembrane protein or the sequence encoding the mature protein if the protein is extracellular) is amplified by PCR with primers complementary to the 5' and 3' regions. The 5' primer may incorporate flanking (selected) restriction enzyme sites. The product is then digested with those selected restriction enzymes and subcloned into the expression vector.

Recombinant baculovirus is generated by co-transfecting the above plasmid and BaculoGold™ virus DNA (Pharmingen) into *Spodoptera frugiperda* ("Sf9") cells (ATCC CRL 1711) using lipofectin (commercially available from GIBCO-BRL). After 4 - 5 days of incubation at 28°C, the released viruses are harvested and used for further amplifications. Viral infection and protein expression are performed as described by O'Reilley *et al.*, Baculovirus expression vectors: A Laboratory Manual, Oxford: Oxford University Press (1994).

Expressed poly-His tagged PRO can then be purified, for example, by Ni<sup>2+</sup>-chelate affinity chromatography as follows. Extracts are prepared from recombinant virus-infected Sf9 cells as described by Rupert *et al.*, Nature, 362:175-179 (1993). Briefly, Sf9 cells are washed, resuspended in sonication buffer (25 ml Hepes, pH 7.9; 12.5 mM MgCl<sub>2</sub>; 0.1 mM EDTA; 10% glycerol; 0.1% NP-40; 0.4 M KCl), and sonicated twice for 20 seconds on ice. The sonicates are cleared by centrifugation, and the supernatant is diluted 50-fold in loading buffer (50 mM phosphate, 300 mM NaCl, 10% glycerol, pH 7.8) and filtered through a 0.45 µm filter. A Ni<sup>2+</sup>-NTA agarose column (commercially available from Qiagen) is prepared with a bed volume of 5 ml, washed with 25 ml of water and equilibrated with 25 ml of loading buffer. The filtered cell extract is loaded onto the column at 0.5 ml per minute. The column is washed to baseline A<sub>280</sub> with loading buffer, at which point fraction collection is started. Next, the column is washed with a secondary wash buffer (50 mM phosphate; 300 mM NaCl, 10% glycerol, pH 6.0), which elutes nonspecifically bound protein. After reaching A<sub>280</sub> baseline again, the column is developed with a 0 to 500 mM imidazole gradient in the secondary wash buffer. One ml fractions are collected and analyzed by SDS-PAGE and silver staining or Western blot with Ni<sup>2+</sup>-NTA-conjugated to alkaline phosphatase (Qiagen). Fractions containing the eluted His<sub>10</sub>-tagged PRO are pooled and dialyzed against loading buffer.

Alternatively, purification of the IgG tagged (or Fc tagged) PRO can be performed using known chromatography techniques, including for instance, Protein A or protein G column chromatography.

Following PCR amplification, the respective coding sequences are subcloned into a baculovirus expression vector (pb.PH.IgG for IgG fusions and pb.PH.His.c for poly-His tagged proteins), and the vector and Baculogold® baculovirus DNA (Pharmingen) are co-transfected into 105 *Spodoptera frugiperda* ("Sf9") cells (ATCC CRL 1711), using Lipofectin (Gibco BRL). pb.PH.IgG and pb.PH.His are modifications of the commercially available baculovirus expression vector pVL1393 (Pharmingen), with modified polylinker regions to include the His or Fc tag sequences. The cells are grown in Hink's TNM-FH medium supplemented with 10% FBS (Hyclone). Cells are

incubated for 5 days at 28°C. The supernatant is harvested and subsequently used for the first viral amplification by infecting Sf9 cells in Hink's TNM-FH medium supplemented with 10% FBS at an approximate multiplicity of infection (MOI) of 10. Cells are incubated for 3 days at 28°C. The supernatant is harvested and the expression of the constructs in the baculovirus expression vector is determined by batch binding of 1 ml of supernatant to 25 ml of Ni<sup>2+</sup>-NTA beads (QIAGEN) for histidine tagged proteins or Protein-A Sepharose CL-4B beads (Pharmacia) for IgG tagged proteins followed by SDS-PAGE analysis comparing to a known concentration of protein standard by Coomassie blue staining.

The first viral amplification supernatant is used to infect a spinner culture (500 ml) of Sf9 cells grown in ESF-921 medium (Expression Systems LLC) at an approximate MOI of 0.1. Cells are incubated for 3 days at 28°C. The supernatant is harvested and filtered. Batch binding and SDS-PAGE analysis is repeated, as necessary, until expression of the spinner culture is confirmed.

The conditioned medium from the transfected cells (0.5 to 3 L) is harvested by centrifugation to remove the cells and filtered through 0.22 micron filters. For the poly-His tagged constructs, the protein construct is purified using a Ni<sup>2+</sup>-NTA column (Qiagen). Before purification, imidazole is added to the conditioned media to a concentration of 5 mM. The conditioned media is pumped onto a 6 ml Ni<sup>2+</sup>-NTA column equilibrated in 20 mM Hepes, pH 7.4, buffer containing 0.3 M NaCl and 5 mM imidazole at a flow rate of 4-5 ml/min. at 4°C. After loading, the column is washed with additional equilibration buffer and the protein eluted with equilibration buffer containing 0.25 M imidazole. The highly purified protein is subsequently desalted into a storage buffer containing 10 mM Hepes, 0.14 M NaCl and 4% mannitol, pH 6.8, with a 25 ml G25 Superfine (Pharmacia) column and stored at -80°C.

Immunoadhesin (Fc containing) constructs of proteins are purified from the conditioned media as follows. The conditioned media is pumped onto a 5 ml Protein A column (Pharmacia) which has been equilibrated in 20 mM Na phosphate buffer, pH 6.8. After loading, the column is washed extensively with equilibration buffer before elution with 100 mM citric acid, pH 3.5. The eluted protein is immediately neutralized by collecting 1 ml fractions into tubes containing 275 ml of 1 M Tris buffer, pH 9. The highly purified protein is subsequently desalted into storage buffer as described above for the poly-His tagged proteins. The homogeneity of the proteins is verified by SDS polyacrylamide gel (PAGE) electrophoresis and N-terminal amino acid sequencing by Edman degradation.

Alternatively, a modified baculovirus procedure may be used incorporating high-5 cells. In this procedure, the DNA encoding the desired sequence is amplified with suitable systems, such as Pfu (Stratagene), or fused upstream (5'-of) of an epitope tag contained with a baculovirus expression vector. Such epitope tags include poly-His tags and immunoglobulin tags (like Fc regions of IgG). A variety of plasmids may be employed, including plasmids derived from commercially available plasmids such as pIE1-1 (Novagen). The pIE1-1 and pIE1-2 vectors are designed for constitutive expression of recombinant proteins from the baculovirus ie1 promoter in stably-transformed insect cells (1). The plasmids differ only in the orientation of the multiple cloning sites and contain all promoter sequences known to be important for ie1-mediated gene expression in uninfected insect cells as well as the hr5 enhancer element. pIE1-1 and pIE1-2 include the translation initiation site and can be used to produce fusion proteins. Briefly, the desired sequence or the desired portion of the sequence (such as the sequence encoding the

extracellular domain of a transmembrane protein) is amplified by PCR with primers complementary to the 5' and 3' regions. The 5' primer may incorporate flanking (selected) restriction enzyme sites. The product is then digested with those selected restriction enzymes and subcloned into the expression vector. For example, derivatives of pIE1-1 can include the Fc region of human IgG (pb.PH.IgG) or an 8 histidine (pb.PH.His) tag downstream (3'-of) the desired sequence. Preferably, the vector construct is sequenced for confirmation.

High-5 cells are grown to a confluency of 50% under the conditions of, 27°C, no CO<sub>2</sub>, NO pen/strep. For each 150 mm plate, 30 µg of pIE based vector containing the sequence is mixed with 1 ml Ex-Cell medium (Media: Ex-Cell 401 + 1/100 L-Glu JRH Biosciences #14401-78P (note: this media is light sensitive)), and in a separate tube, 100 µl of CellFectin (CellFECTIN (GibcoBRL #10362-010) (vortexed to mix)) is mixed with 1 ml of Ex-Cell medium. The two solutions are combined and allowed to incubate at room temperature for 15 minutes. 8 ml of Ex-Cell media is added to the 2 ml of DNA/CellFECTIN mix and this is layered on high-5 cells that have been washed once with Ex-Cell media. The plate is then incubated in darkness for 1 hour at room temperature. The DNA/CellFECTIN mix is then aspirated, and the cells are washed once with Ex-Cell to remove excess CellFECTIN, 30 ml of fresh Ex-Cell media is added and the cells are incubated for 3 days at 28°C. The supernatant is harvested and the expression of the sequence in the baculovirus expression vector is determined by batch binding of 1 ml of supernatant to 25 ml of Ni<sup>2+</sup>-NTA beads (QIAGEN) for histidine tagged proteins or Protein-A Sepharose CL-4B beads (Pharmacia) for IgG tagged proteins followed by SDS-PAGE analysis comparing to a known concentration of protein standard by Coomassie blue staining.

The conditioned media from the transfected cells (0.5 to 3 L) is harvested by centrifugation to remove the cells and filtered through 0.22 micron filters. For the poly-His tagged constructs, the protein comprising the sequence is purified using a Ni<sup>2+</sup>-NTA column (Qiagen). Before purification, imidazole is added to the conditioned media to a concentration of 5 mM. The conditioned media is pumped onto a 6 ml Ni<sup>2+</sup>-NTA column equilibrated in 20 mM Hepes, pH 7.4, buffer containing 0.3 M NaCl and 5 mM imidazole at a flow rate of 4-5 ml/min. at 48°C. After loading, the column is washed with additional equilibration buffer and the protein eluted with equilibration buffer containing 0.25 M imidazole. The highly purified protein is then subsequently desalted into a storage buffer containing 10 mM Hepes, 0.14 M NaCl and 4% mannitol, pH 6.8, with a 25 ml G25 Superfine (Pharmacia) column and stored at -80°C.

Immunoadhesin (Fc containing) constructs of proteins are purified from the conditioned media as follows. The conditioned media is pumped onto a 5 ml Protein A column (Pharmacia) which had been equilibrated in 20 mM Na phosphate buffer, pH 6.8. After loading, the column is washed extensively with equilibration buffer before elution with 100 mM citric acid, pH 3.5. The eluted protein is immediately neutralized by collecting 1 ml fractions into tubes containing 275 ml of 1 M Tris buffer, pH 9. The highly purified protein is subsequently desalted into storage buffer as described above for the poly-His tagged proteins. The homogeneity of the sequence is assessed by SDS polyacrylamide gels and by N-terminal amino acid sequencing by Edman degradation and other analytical procedures as desired or necessary.

Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

#### 6.11. EXAMPLE 11: Preparation of Antibodies that Bind PRO

This example illustrates preparation of monoclonal antibodies which can specifically bind the PRO polypeptide or an epitope on the PRO polypeptide without substantially binding to any other polypeptide or polypeptide epitope.

5 Techniques for producing the monoclonal antibodies are known in the art and are described, for instance, in Goding, *supra*. Immunogens that may be employed include purified PRO, fusion proteins containing PRO, and cells expressing recombinant PRO on the cell surface. Selection of the immunogen can be made by the skilled artisan without undue experimentation.

10 Mice, such as Balb/c, are immunized with the PRO immunogen emulsified in complete Freund's adjuvant and injected subcutaneously or intraperitoneally in an amount from 1-100 micrograms. Alternatively, the immunogen is emulsified in MPL-TDM adjuvant (Ribi Immunochemical Research, Hamilton, MT) and injected into the animal's hind foot pads. The immunized mice are then boosted 10 to 12 days later with additional immunogen emulsified in the selected adjuvant. Thereafter, for several weeks, the mice may also be boosted with additional immunization injections. Serum samples may be periodically obtained from the mice by retro-orbital  
15 bleeding for testing in ELISA assays to detect anti-PRO antibodies.

After a suitable antibody titer has been detected, the animals "positive" for antibodies can be injected with a final intravenous injection of PRO. Three to four days later, the mice are sacrificed and the spleen cells are harvested. The spleen cells are then fused (using 35% polyethylene glycol) to a selected murine myeloma cell line such as P3X63AgU.1, available from ATCC, No. CRL 1597. The fusions generate hybridoma cells which can then  
20 be plated in 96 well tissue culture plates containing HAT (hypoxanthine, aminopterin, and thymidine) medium to inhibit proliferation of non-fused cells, myeloma hybrids, and spleen cell hybrids.

The hybridoma cells will be screened in an ELISA for reactivity against PRO. Determination of "positive" hybridoma cells secreting the desired monoclonal antibodies against PRO is within the skill in the art.

25 The positive hybridoma cells can be injected intraperitoneally into syngeneic Balb/c mice to produce ascites containing the anti-PRO monoclonal antibodies. Alternatively, the hybridoma cells can be grown in tissue culture flasks or roller bottles. Purification of the monoclonal antibodies produced in the ascites can be accomplished using ammonium sulfate precipitation, followed by gel exclusion chromatography. Alternatively, affinity chromatography based upon binding of antibody to protein A or protein G can be employed.

#### 6.12. EXAMPLE 12: Purification of PRO Polypeptides Using Specific Antibodies

30 Native or recombinant PRO polypeptides may be purified by a variety of standard techniques in the art of protein purification. For example, pro-PRO polypeptide, mature PRO polypeptide, or pre-PRO polypeptide is purified by immunoaffinity chromatography using antibodies specific for the PRO polypeptide of interest. In general, an immunoaffinity column is constructed by covalently coupling the anti-PRO polypeptide antibody to an activated chromatographic resin.

35 Polyclonal immunoglobulins are prepared from immune sera either by precipitation with ammonium sulfate or by purification on immobilized Protein A (Pharmacia LKB Biotechnology, Piscataway, N.J.). Likewise,



monoclonal antibodies are prepared from mouse ascites fluid by ammonium sulfate precipitation or chromatography on immobilized Protein A. Partially purified immunoglobulin is covalently attached to a chromatographic resin such as CnBr-activated SEPHAROSE™ (Pharmacia LKB Biotechnology). The antibody is coupled to the resin, the resin is blocked, and the derivative resin is washed according to the manufacturer's instructions.

Such an immunoaffinity column is utilized in the purification of PRO polypeptide by preparing a fraction from cells containing PRO polypeptide in a soluble form. This preparation is derived by solubilization of the whole cell or of a subcellular fraction obtained via differential centrifugation by the addition of detergent or by other methods well known in the art. Alternatively, soluble PRO polypeptide containing a signal sequence may be secreted in useful quantity into the medium in which the cells are grown.

A soluble PRO polypeptide-containing preparation is passed over the immunoaffinity column, and the column is washed under conditions that allow the preferential absorbance of PRO polypeptide (e.g., high ionic strength buffers in the presence of detergent). Then, the column is eluted under conditions that disrupt antibody/PRO polypeptide binding (e.g., a low pH buffer such as approximately pH 2-3, or a high concentration of a chaotrope such as urea or thiocyanate ion), and PRO polypeptide is collected.

#### 6.13. EXAMPLE 13: Drug Screening

This invention is particularly useful for screening compounds by using PRO polypeptides or binding fragment thereof in any of a variety of drug screening techniques. The PRO polypeptide or fragment employed in such a test may either be free in solution, affixed to a solid support, borne on a cell surface, or located intracellularly. One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant nucleic acids expressing the PRO polypeptide or fragment. Drugs are screened against such transformed cells in competitive binding assays. Such cells, either in viable or fixed form, can be used for standard binding assays. One may measure, for example, the formation of complexes between PRO polypeptide or a fragment and the agent being tested. Alternatively, one can examine the diminution in complex formation between the PRO polypeptide and its target cell or target receptors caused by the agent being tested.

Thus, the present invention provides methods of screening for drugs or any other agents which can affect a PRO polypeptide-associated disease or disorder. These methods comprise contacting such an agent with an PRO polypeptide or fragment thereof and assaying (i) for the presence of a complex between the agent and the PRO polypeptide or fragment, or (ii) for the presence of a complex between the PRO polypeptide or fragment and the cell, by methods well known in the art. In such competitive binding assays, the PRO polypeptide or fragment is typically labeled. After suitable incubation, free PRO polypeptide or fragment is separated from that present in bound form, and the amount of free or uncomplexed label is a measure of the ability of the particular agent to bind to PRO polypeptide or to interfere with the PRO polypeptide/cell complex.

Another technique for drug screening provides high throughput screening for compounds having suitable binding affinity to a polypeptide and is described in detail in WO 84/03564, published on September 13, 1984. Briefly stated, large numbers of different small peptide test compounds are synthesized on a solid substrate, such

as plastic pins or some other surface. As applied to a PRO polypeptide, the peptide test compounds are reacted with PRO polypeptide and washed. Bound PRO polypeptide is detected by methods well known in the art. Purified PRO polypeptide can also be coated directly onto plates for use in the aforementioned drug screening techniques. In addition, non-neutralizing antibodies can be used to capture the peptide and immobilize it on the solid support.

This invention also contemplates the use of competitive drug screening assays in which neutralizing antibodies capable of binding PRO polypeptide specifically compete with a test compound for binding to PRO polypeptide or fragments thereof. In this manner, the antibodies can be used to detect the presence of any peptide which shares one or more antigenic determinants with PRO polypeptide.

#### 6.14. EXAMPLE 14: Rational Drug Design

The goal of rational drug design is to produce structural analogs of biologically active polypeptide of interest (*i.e.*, a PRO polypeptide) or of small molecules with which they interact, *e.g.*, agonists, antagonists, or inhibitors. Any of these examples can be used to fashion drugs which are more active or stable forms of the PRO polypeptide or which enhance or interfere with the function of the PRO polypeptide *in vivo* (*c.f.*, Hodgson, Bio/Technology, 2: 19-21 (1991)).

In one approach, the three-dimensional structure of the PRO polypeptide, or of an PRO polypeptide-inhibitor complex, is determined by x-ray crystallography, by computer modeling or, most typically, by a combination of the two approaches. Both the shape and charges of the PRO polypeptide must be ascertained to elucidate the structure and to determine active site(s) of the molecule. Less often, useful information regarding the structure of the PRO polypeptide may be gained by modeling based on the structure of homologous proteins. In both cases, relevant structural information is used to design analogous PRO polypeptide-like molecules or to identify efficient inhibitors. Useful examples of rational drug design may include molecules which have improved activity or stability as shown by Braxton and Wells, Biochemistry, 31:7796-7801 (1992) or which act as inhibitors, agonists, or antagonists of native peptides as shown by Athauda *et al.*, J. Biochem., 113:742-746 (1993).

It is also possible to isolate a target-specific antibody, selected by functional assay, as described above, and then to solve its crystal structure. This approach, in principle, yields a pharmacore upon which subsequent drug design can be based. It is possible to bypass protein crystallography altogether by generating anti-idiotypic antibodies (anti-ids) to a functional, pharmacologically active antibody. As a mirror image of a mirror image, the binding site of the anti-ids would be expected to be an analog of the original receptor. The anti-id could then be used to identify and isolate peptides from banks of chemically or biologically produced peptides. The isolated peptides would then act as the pharmacore.

By virtue of the present invention, sufficient amounts of the PRO polypeptide may be made available to perform such analytical studies as X-ray crystallography. In addition, knowledge of the PRO polypeptide amino acid sequence provided herein will provide guidance to those employing computer modeling techniques in place of or in addition to x-ray crystallography.

6.15. EXAMPLE 15: Stimulation of Endothelial Cell Proliferation (Assay 8)

This assay is designed to determine whether PRO polypeptides of the present invention show the ability to stimulate adrenal cortical capillary endothelial cell (ACE) growth. PRO polypeptides testing positive in this assay would be expected to be useful for the therapeutic treatment of conditions or disorders where angiogenesis would be beneficial including, for example, wound healing, and the like (as would agonists of these PRO polypeptides). Antagonists of the PRO polypeptides testing positive in this assay would be expected to be useful for the therapeutic treatment of cancerous tumors.

Bovine adrenal cortical capillary endothelial (ACE) cells (from primary culture, maximum of 12-14 passages) were plated in 96-well plates at 500 cells/well per 100 microliter. Assay media included low glucose DMEM, 10% calf serum, 2 mM glutamine, and 1X penicillin/streptomycin/fungizone. Control wells included the following: (1) no ACE cells added; (2) ACE cells alone; (3) ACE cells plus VEGF (5 ng/ml); and (4) ACE cells plus FGF (5ng/ml). The control or test sample, (in 100 microliter volumes), was then added to the wells (at dilutions of 1%, 0.1% and 0.01%, respectively). The cell cultures were incubated for 6-7 days at 37°C/5% CO<sub>2</sub>. After the incubation, the media in the wells was aspirated, and the cells were washed 1X with PBS. An acid phosphatase reaction mixture (100 microliter, 0.1M sodium acetate, pH 5.5, 0.1% Triton X-100, 10 mM p-nitrophenyl phosphate) was then added to each well. After a 2 hour incubation at 37°C, the reaction was stopped by addition of 10 microliters 1N NaOH. Optical density (OD) was measured on a microplate reader at 405 nm.

The activity of a PRO polypeptide was calculated as the fold increase in proliferation (as determined by the acid phosphatase activity, OD 405 nm) relative to (1) cell only background, and (2) relative to maximum stimulation by VEGF. VEGF (at 3-10 ng/ml) and FGF (at 1-5 ng/ml) were employed as an activity reference for maximum stimulation. Results of the assay were considered "positive" if the observed stimulation was  $\geq$  50% increase over background. VEGF (5 ng/ml) control at 1% dilution gave 1.24 fold stimulation; FGF (5 ng/ml) control at 1% dilution gave 1.46 fold stimulation.

PRO21 tested positive in this assay.

6.16. EXAMPLE 16: Inhibition of Vascular Endothelial Growth Factor (VEGF) Stimulated Proliferation of Endothelial Cell Growth (Assay 9)

The ability of various PRO polypeptides to inhibit VEGF stimulated proliferation of endothelial cells was tested. Polypeptides testing positive in this assay are useful for inhibiting endothelial cell growth in mammals where such an effect would be beneficial, e.g., for inhibiting tumor growth.

Specifically, bovine adrenal cortical capillary endothelial cells (ACE) (from primary culture, maximum of 12-14 passages) were plated in 96-well plates at 500 cells/well per 100 microliter. Assay media included low glucose DMEM, 10% calf serum, 2 mM glutamine, and 1X penicillin/streptomycin/fungizone. Control wells included the following: (1) no ACE cells added; (2) ACE cells alone; (3) ACE cells plus 5 ng/ml FGF; (4) ACE cells plus 3 ng/ml VEGF; (5) ACE cells plus 3 ng/ml VEGF plus 1 ng/ml TGF-beta; and (6) ACE cells plus 3 ng/ml VEGF plus 5 ng/ml LIF. The test samples, poly-his tagged PRO polypeptides (in 100 microliter volumes), were then added to the wells (at dilutions of 1%, 0.1% and 0.01%, respectively). The cell cultures were

incubated for 6-7 days at 37°C/5% CO<sub>2</sub>. After the incubation, the media in the wells was aspirated, and the cells were washed 1X with PBS. An acid phosphatase reaction mixture (100 microliter; 0.1M sodium acetate, pH 5.5, 0.1% Triton X-100, 10 mM p-nitrophenyl phosphate) was then added to each well. After a 2 hour incubation at 37°C, the reaction was stopped by addition of 10 microliters 1N NaOH. Optical density (OD) was measured on a microplate reader at 405 nm.

The activity of PRO polypeptides was calculated as the percent inhibition of VEGF (3 ng/ml) stimulated proliferation (as determined by measuring acid phosphatase activity at OD 405 nm) relative to the cells without stimulation. TGF-beta was employed as an activity reference at 1 ng/ml, since TGF-beta blocks 70-90% of VEGF-stimulated ACE cell proliferation. The results are indicative of the utility of the PRO polypeptides in cancer therapy and specifically in inhibiting tumor angiogenesis. Numerical values (relative inhibition) are determined by calculating the percent inhibition of VEGF stimulated proliferation by the PRO polypeptides relative to cells without stimulation and then dividing that percentage into the percent inhibition obtained by TGF-β at 1 ng/ml which is known to block 70-90% of VEGF stimulated cell proliferation. The results are considered positive if the PRO polypeptide exhibits 30% or greater inhibition of VEGF stimulation of endothelial cell growth (relative inhibition 30% or greater).

PRO247, PRO720 and PRO4302 tested positive in this assay.

6.17. EXAMPLE 17: Enhancement of Heart Neonatal Hypertrophy Induced by LIF+ET-1 (Assay 75)

This assay is designed to determine whether PRO polypeptides of the present invention show the ability to enhance neonatal heart hypertrophy induced by LIF and endothelin-1 (ET-1). A test compound that provides a positive response in the present assay would be useful for the therapeutic treatment of cardiac insufficiency diseases or disorders characterized or associated with an undesired level of hypertrophy of the cardiac muscle.

Cardiac myocytes from 1-day old Harlan Sprague Dawley rats (180 μl at 7.5 x 10<sup>4</sup>/ml, serum <0.1, freshly isolated) are introduced on day 1 to 96-well plates previously coated with DMEM/F12 + 4%FCS. Test PRO polypeptide samples or growth medium alone (negative control) are then added directly to the wells on day 2 in 20 μl volume. LIF + ET-1 are then added to the wells on day 3. The cells are stained after an additional 2 days in culture and are then scored visually the next day. A positive in the assay occurs when the PRO polypeptide treated myocytes obtain a score greater than zero. A score of zero represents non-responsive cells whereas scores of 1 or 2 represent enhancement (*i.e.* they are visually larger on the average or more numerous than the untreated myocytes).

PRO21 polypeptides tested positive in this assay.

6.18. EXAMPLE 18: Detection of Endothelial Cell Apoptosis (FACS) (Assay 96)

The ability of PRO polypeptides of the present invention to induce apoptosis in endothelial cells was tested in human venous umbilical vein endothelial cells (HUVEC, Cell Systems) in gelatinized T175 flasks using HUVEC cells below passage 10. PRO polypeptides testing positive in this assay are expected to be useful for

therapeutically treating conditions where apoptosis of endothelial cells would be beneficial including, for example, the therapeutic treatment of tumors.

On day one, the cells were split [420,000 cells per gelatinized 6 cm dishes - (11 x 10<sup>3</sup> cells/cm<sup>2</sup> Falcon, Primaria)] and grown in media containing serum (CS-C, Cell System) overnight or for 16 hours to 24 hours.

On day 2, the cells were washed 1x with 5 ml PBS ; 3 ml of 0% serum medium was added with VEGF (100 ng/ml); and 30  $\mu$ l of the PRO test compound (final dilution 1%) or 0% serum medium (negative control) was added. The mixtures were incubated for 48 hours before harvesting.

The cells were then harvested for FACS analysis. The medium was aspirated and the cells washed once with PBS. 5 ml of 1 x trypsin was added to the cells in a T-175 flask, and the cells were allowed to stand until they were released from the plate (about 5-10 minutes). Trypsinization was stopped by adding 5 ml of growth media. The cells were spun at 1000 rpm for 5 minutes at 4°C. The media was aspirated and the cells were resuspended in 10 ml of 10% serum complemented medium (Cell Systems), 5  $\mu$ l of Annexin-FITC (BioVison) added and chilled tubes were submitted for FACS. A positive result was determined to be enhanced apoptosis in the PRO polypeptide treated samples as compared to the negative control.

PRO4302 polypeptide tested positive in this assay.

#### 6.19. EXAMPLE 19: Induction of c-fos in HUVEC Cells (Assay 123)

This assay is designed to determine whether PRO polypeptides show the ability to induce c-fos in HUVEC cells. PRO polypeptides testing positive in this assay would be expected to be useful for the therapeutic treatment of conditions or disorders where angiogenesis would be beneficial including, for example, wound healing, and the like (as would agonists of these PRO polypeptides). Antagonists of the PRO polypeptides testing positive in this assay would be expected to be useful for the therapeutic treatment of cancerous tumors.

Human venous umbilical vein endothelial cells (HUVEC, Cell Systems) in growth media (50% Ham's F12 w/o GHT: low glucose, and 50% DMEM without glycine: with NaHCO<sub>3</sub>, 1% glutamine, 10 mM HEPES, 10% FBS, 10 ng/ml bFGF) were plated on 96-well microtiter plates at a cell density of 5x10<sup>3</sup> cells/well. The day after plating (day 2), the cells were starved for 24 hours by removing the growth media and replacing with serum free media. On day 3, the cells are treated with 100  $\mu$ l/well test samples and controls (positive control = growth media; negative control = Protein 32 buffer = 10 mM HEPES, 140 mM NaCl, 4% (w/v) mannitol, pH 6.8). One plate of cells was incubated for 30 minutes at 37°C, in 5% CO<sub>2</sub>. Another plate of cells was incubated for 60 minutes at 37°C, in 5% CO<sub>2</sub>. The samples were removed, and RNA was harvested using the RNeasy 96 kit (Qiagen). Next, the RNA was assayed for c-fos, egr-1 and GAPDH induction using Taqman.

The measure of activity of the fold increase over the negative control (Protein 32/HEPES buffer described above) value was by obtained by calculating the fold increase of the ratio of c-fos to GAPDH in test samples as compared to the negative control. The results are considered positive if the PRO polypeptide exhibits at least a two-fold value over the negative buffer control.

PRO1376 polypeptide tested positive in this assay.

6.20. EXAMPLE 20: Normal Human Iliac Artery Endothelial Cell Proliferation (Assay 138)

This assay is designed to determine whether PRO polypeptides of the present invention show the ability to modulate proliferation of human iliac artery endothelial cells in culture and, therefore, function as useful growth or inhibitory factors.

On day 0, human iliac artery endothelial cells (from cell lines, maximum of 12-14 passages) were plated in 96-well plates at 1000 cells/well per 100 microliter and incubated overnight in complete media [epithelial cell growth media (EGM, Clonetics), plus supplements: human epithelial growth factor (hEGF), bovine brain extract (BBE), hydrocortisone, GA-1000, and fetal bovine serum (FBS, Clonetics)]. On day 1, complete media was replaced by basal media [EGM plus 1% FBS] and addition of PRO polypeptides at 1%, 0.1% and 0.01%. On day 7, an assessment of cell proliferation was performed by Alamar Blue assay followed by Crystal Violet. Results are expressed as % of the cell growth observed with control buffer.

The following PRO polypeptides stimulated proliferation in this assay: PRO214, PRO256, PRO363, PRO365, PRO791, PRO836, PRO1025, PRO1186, PRO1192, PRO1272, PRO1306, PRO1325, PRO1329, PRO1376, PRO1411, PRO1508, PRO1787, PRO1868, PRO4324, PRO4333, PRO4408, PRO4499, PRO9821, PRO9873, PRO10008, PRO10096, PRO19670, PRO20040, PRO20044 and PRO21384.

The following PRO polypeptides inhibited proliferation in this assay: PRO238, PRO1029, PRO1274, PRO1279, PRO1419, PRO1890, PRO6006 and PRO28631.

6.21. EXAMPLE 21: Pooled Human Umbilical Vein Endothelial Cell Proliferation (Assay 139)

This assay is designed to determine whether PRO polypeptides of the present invention show the ability to modulate proliferation of pooled human umbilical vein endothelial cells in culture and, therefore, function as useful growth or inhibitory factors.

On day 0, pooled human umbilical vein endothelial cells (from cell lines, maximum of 12-14 passages) were plated in 96-well plates at 1000 cells/well per 100 microliter and incubated overnight in complete media [epithelial cell growth media (EGM, Clonetics), plus supplements: human epithelial growth factor (hEGF), bovine brain extract (BBE), hydrocortisone, GA-1000, and fetal bovine serum (FBS, Clonetics)]. On day 1, complete media was replaced by basal media [EGM plus 1% FBS] and addition of PRO polypeptides at 1%, 0.1% and 0.01%. On day 7, an assessment of cell proliferation was performed by Alamar Blue assay followed by Crystal Violet. Results are expressed as % of the cell growth observed with control buffer.

The following PRO polypeptides stimulated proliferation in this assay: PRO181, PRO205, PRO221, PRO231, PRO238, PRO241, PRO247, PRO256, PRO258, PRO263, PRO265, PRO295, PRO321, PRO322, PRO337, PRO363, PRO533, PRO697, PRO725, PRO771, PRO788, PRO819, PRO828, PRO846, PRO865, PRO1005, PRO1006, PRO1025, PRO1054, PRO1071, PRO1079, PRO1080, PRO1114, PRO1131, PRO1155, PRO1160, PRO1192, PRO1244, PRO1272, PRO1273, PRO1279, PRO1283, PRO1286, PRO1306, PRO1309, PRO1325, PRO1329, PRO1347, PRO1356, PRO1376, PRO1382, PRO1412, PRO1550, PRO1556, PRO1760, PRO1787, PRO1801, PRO1868, PRO1887, PRO3438, PRO3444, PRO4324, PRO4341, PRO4342, PRO4353,

PRO4354, PRO4356, PRO4371, PRO4422, PRO4425, PRO5723, PRO5737, PRO6029, PRO6071, PRO10096 and PRO21055.

The following PRO polypeptides inhibited proliferation in this assay: PRO229, PRO444, PRO827, PRO1007, PRO1075, PRO1184, PRO1190, PRO1195, PRO1419, PRO1474, PRO1477, PRO1488, PRO1782, PRO4302, PRO4405, PRO5725, PRO5776, PRO7436, PRO9771, PRO10008 and PRO21384.

#### 6.22. EXAMPLE 22: Human Coronary Artery Smooth Muscle Cell Proliferation (Assay 140)

This assay is designed to determine whether PRO polypeptides of the present invention show the ability to modulate proliferation of human coronary artery smooth muscle cells in culture and, therefore, function as useful growth or inhibitory factors.

On day 0, human coronary artery smooth muscle cells (from cell lines, maximum of 12-14 passages) were plated in 96-well plates at 1000 cells/well per 100 microliter and incubated overnight in complete media [smooth muscle growth media (SmGM, Clonetics), plus supplements: insulin, human epithelial growth factor (hEGF), human fibroblast growth factor (hFGF), GA-1000, and fetal bovine serum (FBS, Clonetics)]. On day 1, complete media was replaced by basal media [SmGM plus 1% FBS] and addition of PRO polypeptides at 1%, 0.1% and 0.01%. On day 7, an assessment of cell proliferation was performed by Alamar Blue assay followed by Crystal Violet. Results are expressed as % of the cell growth observed with control buffer.

The following PRO polypeptides stimulated proliferation in this assay: PRO162, PRO182, PRO204, PRO221, PRO230, PRO256, PRO258, PRO533, PRO697, PRO725, PRO738, PRO826, PRO836, PRO840, PRO846, PRO865, PRO982, PRO1025, PRO1029, PRO1071, PRO1083, PRO1134, PRO1160, PRO1182, PRO1184, PRO1186, PRO1192, PRO1274, PRO1279, PRO1283, PRO1306, PRO1308, PRO1325, PRO1337, PRO1338, PRO1343, PRO1376, PRO1387, PRO1411, PRO1412, PRO1415, PRO1434, PRO1474, PRO1550, PRO1556, PRO1567, PRO1600, PRO1754, PRO1758, PRO1760, PRO1787, PRO1865, PRO1868, PRO1917, PRO1928, PRO3438, PRO3562, PRO4333, PRO4345, PRO4353, PRO4354, PRO4408, PRO4430, PRO4503, PRO6714, PRO9771, PRO9820, PRO9940, PRO10096, PRO21055, PRO21184 and PRO21366.

The following PRO polypeptides inhibited proliferation in this assay: PRO181, PRO195, PRO1080, PRO1265, PRO1309, PRO1488, PRO4302, PRO4405 and PRO5725.

#### 6.23. EXAMPLE 23: Microarray Analysis to Detect Overexpression of PRO Polypeptides in HUVEC Cells Treated with Growth Factors

This assay is designed to determine whether PRO polypeptides of the present invention show the ability to induce angiogenesis by stimulating endothelial cell tube formation in HUVEC cells.

Nucleic acid microarrays, often containing thousands of gene sequences, are useful for identifying differentially expressed genes in tissues exposed to various stimuli (*e.g.*, growth factors) as compared to their normal, unexposed counterparts. Using nucleic acid microarrays, test and control mRNA samples from test and control tissue samples are reverse transcribed and labeled to generate cDNA probes. The cDNA probes are then hybridized to an array of nucleic acids immobilized on a solid support. The array is configured such that the

sequence and position of each member of the array is known. Hybridization of a labeled probe with a particular array member indicates that the sample from which the probe was derived expresses that gene. If the hybridization signal of a probe from a test (exposed tissue) sample is greater than hybridization signal of a probe from a control (normal, unexposed tissue) sample, the gene or genes overexpressed in the exposed tissue are identified. The implication of this result is that an overexpressed protein in an exposed tissue may be involved in the functional changes within the tissue following exposure to the stimuli (e.g., tube formation).

The methodology of hybridization of nucleic acids and microarray technology is well known in the art. In the present example, the specific preparation of nucleic acids for hybridization and probes, slides, and hybridization conditions are all detailed in U.S. Provisional Patent Application Serial No. 60/193,767, filed on March 31, 2000 and which is herein incorporated by reference.

In the present example, HUVEC cells grown in either collagen gels or fibrin gels were induced to form tubes by the addition of various growth factors. Specifically, collagen gels were prepared as described previously in Yang *et al.*, *American J. Pathology*, 1999, 155(3):887-895 and Xin *et al.*, *American J. Pathology*, 2001, 158(3):1111-1120. Following gelation of the HUVEC cells, 1X basal medium containing M199 supplemented with 1%FBS, 1X ITS, 2 mM L-glutamine, 50 µg/ml ascorbic acid, 26.5 mM NaHCO<sub>3</sub>, 100U/ml penicillin and 100 U/ml streptomycin was added. Tube formation was elicited by the inclusion in the culture media of either a mixture of phorbol myrsitate acetate (50 nM), vascular endothelial cell growth factor (40 ng/ml) and basic fibroblast growth factor (40 ng/ml) ("PMA growth factor mix") or hepatocyte growth factor (40 ng/ml) and vascular endothelial cell growth factor (40 ng/ml) (HGF/VEGF mix) for the indicated period of time. Fibrin Gels were prepared by suspending Huvec (4 x 10<sup>5</sup> cells/ml) in M199 containing 1% fetal bovine serum (Hyclone) and human fibrinogen (2.5mg/ml). Thrombin (50U/ml) was then added to the fibrinogen suspension at a ratio of 1 part thrombin solution:30 parts fibrinogen suspension. The solution was then layered onto 10 cm tissue culture plates (total volume: 15 ml/plate) and allowed to solidify at 37°C for 20 min. Tissue culture media (10 ml of BM containing PMA (50 nM), bFGF (40ng/ml) and VEGF (40 ng/ml)) was then added and the cells incubated at 37°C in 5%CO<sub>2</sub> in air for the indicated period of time.

Total RNA was extracted from the HUVEC cells incubated for 0, 4, 8, 24, 40 and 50 hours in the different matrix and media combinations using a TRIzol extraction followed by a second purification using RNAeasy Mini Kit (Qiagen). The total RNA was used to prepare cRNA which was then hybridized to the microarrays.

In the present experiments, nucleic acid probes derived from the herein described PRO polypeptide-encoding nucleic acid sequences were used in the creation of the microarray and RNA from the HUVEC cells described above were used for the hybridization thereto. Pairwise comparisons were made using time 0 chips as a baseline. Three replicate samples were analyzed for each experimental condition and time. Hence there were 3 time 0 samples for each treatment and 3 replicates of each successive time point. Therefore, a 3 by 3 comparison was performed for each time point compared against each time 0 point. This resulted in 9 comparisons per time point. Only those genes that had increased expression in all three non-time-0 replicates in each of the different matrix and media combinations as compared to any of the three time zero replicates were



considered positive. Although this stringent method of data analysis does allow for false negatives, it minimizes false positives.

PRO178, PRO195, PRO228, PRO301, PRO302, PRO532, PRO724, PRO730, PRO734, PRO793, PRO871, PRO938, PRO1012, PRO1120, PRO1139, PRO1198, PRO1287, PRO1361, PRO1864, PRO1873, PRO2010, PRO3579, PRO4313, PRO4527, PRO4538, PRO4553, PRO4995, PRO5730, PRO6008, PRO7223, PRO7248 and PRO7261 tested positive in this assay.

#### 6.24. EXAMPLE 24: *In situ* Hybridization

*In situ* hybridization is a powerful and versatile technique for the detection and localization of nucleic acid sequences within cell or tissue preparations. It may be useful, for example, to identify sites of gene expression, analyze the tissue distribution of transcription, identify and localize viral infection, follow changes in specific mRNA synthesis, and aid in chromosome mapping.

*In situ* hybridization was performed following an optimized version of the protocol by Lu and Gillett, Cell Vision, 1: 169-176 (1994), using PCR-generated <sup>33</sup>P-labeled riboprobes. Briefly, formalin-fixed, paraffin-embedded human tissues were sectioned, deparaffinized, deproteinized in proteinase K (20 g/ml) for 15 minutes at 37°C, and further processed for *in situ* hybridization as described by Lu and Gillett, *supra*. A (<sup>33</sup>-P)UTP-labeled antisense riboprobe was generated from a PCR product and hybridized at 55°C overnight. The slides were dipped in Kodak NTB2™ nuclear track emulsion and exposed for 4 weeks.

##### 6.24.1. <sup>33</sup>P-Riboprobe synthesis

6.0 µl (125 mCi) of <sup>33</sup>P-UTP (Amersham BF 1002, SA < 2000 Ci/mmol) were speed-vacuum dried. To each tube containing dried <sup>33</sup>P-UTP, the following ingredients were added:

2.0 µl 5x transcription buffer

1.0 µl DTT (100 mM)

2.0 µl NTP mix (2.5 mM: 10 µl each of 10 mM GTP, CTP & ATP + 10 µl H<sub>2</sub>O)

1.0 µl UTP (50 µM)

1.0 µl RNAsin

1.0 µl DNA template (1 µg)

1.0 µl H<sub>2</sub>O

1.0 µl RNA polymerase (for PCR products T3 = AS, T7 = S, usually)

The tubes were incubated at 37°C for one hour. A total of 1.0 µl RQ1 DNase was added, followed by incubation at 37°C for 15 minutes. A total of 90 µl TE (10 mM Tris pH 7.6/1 mM EDTA pH 8.0) was added, and the mixture was pipetted onto DE81 paper. The remaining solution was loaded in a MICROCON-50™ ultrafiltration unit, and spun using program 10 (6 minutes). The filtration unit was inverted over a second tube and spun using program 2 (3 minutes). After the final recovery spin, a total of 100 µl TE was added, then 1 µl of the final product was pipetted on DE81 paper and counted in 6 ml of BIOFLUOR II™.

The probe was run on a TBE/urea gel. A total of 1-3  $\mu\text{l}$  of the probe or 5  $\mu\text{l}$  of RNA Mrk III was added to 3  $\mu\text{l}$  of loading buffer. After heating on a 95°C heat block for three minutes, the gel was immediately placed on ice. The wells of gel were flushed, and the sample was loaded and run at 180-250 volts for 45 minutes. The gel was wrapped in plastic wrap (SARAN<sup>TM</sup> brand) and exposed to XAR film with an intensifying screen in a -70°C freezer one hour to overnight.

#### 6.24.2. <sup>33</sup>P-Hybridization

##### 6.24.2.1. *Pretreatment of frozen sections*

The slides were removed from the freezer, placed on aluminum trays, and thawed at room temperature for 5 minutes. The trays were placed in a 55°C incubator for five minutes to reduce condensation. The slides were fixed for 10 minutes in 4% paraformaldehyde on ice in the fume hood, and washed in 0.5 x SSC for 5 minutes, at room temperature (25 ml 20 x SSC + 975 ml SQ H<sub>2</sub>O). After deproteinization in 0.5  $\mu\text{g}/\text{ml}$  proteinase K for 10 minutes at 37°C (12.5  $\mu\text{l}$  of 10 mg/ml stock in 250 ml prewarmed RNase-free RNase buffer), the sections were washed in 0.5 x SSC for 10 minutes at room temperature. The sections were dehydrated in 70%, 95%, and 100% ethanol, 2 minutes each.

##### 6.24.2.2. *Pretreatment of paraffin-embedded sections*

The slides were deparaffinized, placed in SQ H<sub>2</sub>O, and rinsed twice in 2 x SSC at room temperature, for 5 minutes each time. The sections were deproteinized in 20  $\mu\text{g}/\text{ml}$  proteinase K (500  $\mu\text{l}$  of 10 mg/ml in 250 ml RNase-free RNase buffer; 37°C, 15 minutes) for human embryo tissue, or 8 x proteinase K (100  $\mu\text{l}$  in 250 ml RNase buffer, 37°C, 30 minutes) for formalin tissues. Subsequent rinsing in 0.5 x SSC and dehydration were performed as described above.

##### 6.24.2.3. *Prehybridization*

The slides were laid out in a plastic box lined with Box buffer (4 x SSC, 50% formamide) - saturated filter paper. The tissue was covered with 50  $\mu\text{l}$  of hybridization buffer (3.75 g dextran sulfate + 6 ml SQ H<sub>2</sub>O), vortexed, and heated in the microwave for 2 minutes with the cap loosened. After cooling on ice, 18.75 ml formamide, 3.75 ml 20 x SSC, and 9 ml SQ H<sub>2</sub>O were added, and the tissue was vortexed well and incubated at 42°C for 1-4 hours.

##### 6.24.2.4. *Hybridization*

1.0 x 10<sup>6</sup> cpm probe and 1.0  $\mu\text{l}$  tRNA (50 mg/ml stock) per slide were heated at 95°C for 3 minutes. The slides were cooled on ice, and 48  $\mu\text{l}$  hybridization buffer was added per slide. After vortexing, 50  $\mu\text{l}$  <sup>33</sup>P mix was added to 50  $\mu\text{l}$  prehybridization on the slide. The slides were incubated overnight at 55°C.

6.24.2.5. *Washes*

Washing was done for 2x10 minutes with 2xSSC, EDTA at room temperature (400 ml 20 x SSC + 16 ml 0.25 M EDTA,  $V_t=4L$ ), followed by RNaseA treatment at 37°C for 30 minutes (500  $\mu$ l of 10 mg/ml in 250 ml Rnase buffer = 20  $\mu$ g/ml). The slides were washed 2 x10 minutes with 2 x SSC, EDTA at room temperature. The stringency wash conditions were as follows: 2 hours at 55°C, 0.1 x SSC, EDTA (20 ml 20 x SSC + 16 ml EDTA,  $V_t=4L$ ).

6.24.2.6. *Oligonucleotides*

*In situ* analysis was performed on three of the DNA sequences disclosed herein. The primers used to generate the probes and/or the probes employed for these analyses are as follows:

- 10 DNA33100-p1: 5'GGA TTC TAA TAC GAC TCA CTA TAG GGC CGG GTG GAG GTG GAA CAG AAA  
3' (SEQ ID NO:375)
- DNA33100-p2: 5' CTA TGA AAT TAA CCC TCA CTA AAG GGA CAC AGA CAG AGC CCC ATA CGC  
3' (SEQ ID NO:376)
- 15 DNA34431-p1: 5'GGA TTC TAA TAC GAC TCA CTA TAG GGC CAG GGA AAT CCG GAT GTC TC  
3' (SEQ ID NO:377)
- DNA34431-p2: 5' CTA TGA AAT TAA CCC TCA CTA AAG GGA GTA AGG GGA TGC CAC CGA GTA  
3' (SEQ ID NO:378)
- DNA38268-p1: 5'GGA TTC TAA TAC GAC TCA CTA TAG GGC CAG CTA CCC GCA GGA GGA GG  
3' (SEQ ID NO:379)
- 20 DNA38268-p2: 5'CTA TGA AAT TAA CCC TCA CTA AAG GGA TCC CAG GTG-ATG AGG TCC AGA  
3' (SEQ ID NO:380)
- DNA64908 probe: 5'CCATCTCGGAGACCTTTGTGCAGCGTGTATACCAGCCTTACCTCACCA  
CTTGCGACGGACACAGAGCCTGCAGCACCTACCGAACCATCTACCGGAC  
TGCCTATCGCCGTAGCCCTGGGGTGACTCCCGCAAGCCTCGCTATGCTTG  
25 CTGCCCTGGTTGGAAGAGGACCAAGTGGGCTCCCTGGGGCTTGTGGAGCA  
GCAATATGCCAGCCTCCATGTGGGAATGGAGGGAGTTGCATCCGCCAG  
GACACTGCCGCTGCCCTGTGGGATGGCAGGGAGATACTTGCCAGACAGA  
TGTTGATGAATGCAGTACAGGAGAGGCCAGTTGTCCCCAGCGCTGTGTC  
AATACTGTGGGAAGTTACTGGTGCCAGGGATGGGAGGGACAAAGCCCAT

CTGCAGATGGGACGCGCTGCCTGTCTAAGGAGGGGCCCTCCCGGTGGCC  
 CCAACCCACAGCAGGAGTGGACAGCA3' (SEQ ID NO:381)

#### 6.24.2.7. Results

*In situ* analysis was performed and the results from these analyses are as follows:

##### 5 6.24.2.7.1. DNA33100-1159 (PRO229) (Scavenger-R/CD6 homologTNF motif)

A specific positive signal was observed in mononuclear phagocytes (macrophages) of fetal and adult spleen, liver, lymph node and thymus. All other tissues were negative.

##### 10 6.24.2.7.2. DNA34431-1177 (PRO263) (CD44)

A specific positive signal was observed in human fetal tissues and placenta over mononuclear cells, with strong expression in epithelial cells of the adrenal cortex. All adult tissues were negative.

##### 6.24.2.7.3. DNA38268-1188 (PRO295) (Integrin)

A specific positive signal was observed in human fetal ganglion cells, fetal neurons, adult adrenal medulla and adult neurons. All other tissues were negative.

##### 15 6.24.2.7.4. DNA64908-1163-1 (PRO1449)

A specific positive signal was observed in the developing vasculature (from E7-E11), in endothelial cells and in progenitors of endothelial cells in wholemount *in situ* hybridizations of mouse embryos (Figure 375). Specific expression was also observed in a subset of blood vessels and epidermis from E12 onward. A mouse orthologue of PRO1449 which has about 78% amino acid identity with PRO1449 was used as the probe.

20 In normal adult tissues, expression was low to absent. When present, expression was confined to the vasculature (Figure 376). Figure 376 further shows that highest expression in adult tissues was observed regionally in vessels running within the white matter of the brain. Elevated expression was also observed in vasculature of many inflamed and diseased tissues, including, but not limited to, tumor vasculature.

25 Following electroporation of the mouse orthologue of PRO1449 into the choroid layer in the eyes of chicken embryos, new vessel formation was observed in the electroporated eye (top right), but not in the control side from the same embryo (top left), or an embryo that was electroporated with a control cDNA (bottom right) (Figure 377).

6.25. EXAMPLE 25: Inhibition of basic Fibroblast Growth Factor (bFGF) Stimulated Proliferation of Endothelial Cell Growth

The ability of various PRO polypeptides to inhibit bFGF stimulated proliferation of endothelial cells was tested. Polypeptides testing positive in this assay are useful for inhibiting endothelial cell growth in mammals where such an effect would be beneficial, e.g., for inhibiting tumor growth.

Specifically, human venous umbilical vein endothelial cells (HUVEC, Cell Systems) in epithelial cell growth media (EGM, Clonetics) were plated on 96-well microtiter plates at a cell density of  $5 \times 10^3$  cells/well in a volume of 100 $\mu$ l/well. The day after plating (day 2), the cells were starved for 24 hours by removing the growth media and replacing with starving media (M199 supplemented with 1% FBS, 2 mM L-glutamine, 100U/ml penicillin and 100 U/ml streptomycin). On day 5, the cells are treated with either: (1) M199 with 10% FBS; (2) M199 with 1% FBS; (3) M199 with 1% FBS and 20 ng/ml bFGF; (4) M199 with 1% FBS and 20 ng/ml bFGF and PRO polypeptide (500 nM); (5) M199 with 1% FBS and 20 ng/ml bFGF and PRO polypeptide (50 nM); or (6) M199 with 1% FBS and 20 ng/ml bFGF and PRO polypeptide (5 nM). On day 8, an assessment of cell proliferation was performed by Alamar Blue assay. Optical density (OD) was measured on a microplate reader at excitation 530 and emission at 590 nm.

The activity of PRO polypeptides was calculated as the percent inhibition of bFGF stimulated proliferation relative to the cells without stimulation. The results are indicative of the utility of the PRO polypeptides in cancer therapy and specifically in inhibiting tumor angiogenesis. Numerical values (relative inhibition) are determined by calculating the percent inhibition of bFGF stimulated proliferation by the PRO polypeptides relative to cells without stimulation. The results are considered positive if the PRO polypeptide exhibits 30% or greater inhibition of bFEGF stimulation of endothelial cell growth.

PRO5725 tested positive in this assay.

The foregoing written specification is considered to be sufficient to enable one skilled in the art to practice the invention. The present invention is not to be limited in scope by the construct(s) deposited, since the deposited embodiment(s) is/are intended as single illustration(s) of certain aspects of the invention and any constructs that are functionally equivalent are within the scope of this invention. The deposit of material(s) herein does not constitute an admission that the written description herein contained is inadequate to enable the practice of any aspect of the invention, including the best mode thereof, nor is it to be construed as limiting the scope of the claims to the specific illustrations that it represents. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and fall within the scope of the appended claims.

WHAT IS CLAIMED IS:

1. An isolated nucleic acid molecule having at least 80% nucleic acid sequence identity to a nucleotide sequence that encodes an amino acid sequence selected from the group consisting of the amino acid sequence shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160), Figure 162 (SEQ ID NO:162), Figure 164 (SEQ ID NO:164), Figure 166 (SEQ ID NO:166), Figure 168 (SEQ ID NO:168), Figure 170 (SEQ ID NO:170), Figure 172 (SEQ ID NO:172), Figure 174 (SEQ ID NO:174), Figure 176 (SEQ ID NO:176), Figure 178 (SEQ ID NO:178), Figure 180 (SEQ ID NO:180), Figure 182 (SEQ ID NO:182), Figure 184 (SEQ ID NO:184), Figure 186 (SEQ ID NO:186), Figure 188 (SEQ ID NO:188), Figure 190 (SEQ ID NO:190), Figure 192 (SEQ ID NO:192), Figure 194 (SEQ ID NO:194), Figure 196 (SEQ ID NO:196), Figure 198 (SEQ ID NO:198), Figure 200 (SEQ ID NO:200), Figure 202 (SEQ ID NO:202), Figure 204 (SEQ ID NO:204), Figure 206 (SEQ ID NO:206), Figure 208 (SEQ ID NO:208), Figure 210 (SEQ ID NO:210), Figure 212 (SEQ ID NO:212), Figure 214 (SEQ ID NO:214), Figure 216 (SEQ ID NO:216), Figure 218 (SEQ ID NO:218), Figure 220 (SEQ ID NO:220), Figure 222 (SEQ ID NO:222), Figure 224 (SEQ ID NO:224), Figure 226 (SEQ ID NO:226), Figure 228 (SEQ ID NO:228), Figure 230 (SEQ ID NO:230), Figure 232 (SEQ ID NO:232), Figure 234 (SEQ ID NO:234), Figure 236 (SEQ ID NO:236), Figure 238 (SEQ ID NO:238), Figure 240 (SEQ ID NO:240), Figure 242 (SEQ ID NO:242), Figure 244 (SEQ ID NO:244), Figure 246 (SEQ ID NO:246), Figure

248 (SEQ ID NO:248), Figure 250 (SEQ ID NO:250), Figure 252 (SEQ ID NO:252), Figure 254 (SEQ ID NO:254), Figure 256 (SEQ ID NO:256), Figure 258 (SEQ ID NO:258), Figure 260 (SEQ ID NO:260), Figure 262 (SEQ ID NO:262), Figure 264 (SEQ ID NO:264), Figure 266 (SEQ ID NO:266), Figure 268 (SEQ ID NO:268), Figure 270 (SEQ ID NO:270), Figure 272 (SEQ ID NO:272), Figure 274 (SEQ ID NO:274), Figure 276 (SEQ ID NO:276), Figure 278 (SEQ ID NO:278), Figure 280 (SEQ ID NO:280), Figure 282 (SEQ ID NO:282), Figure 284 (SEQ ID NO:284), Figure 286 (SEQ ID NO:286), Figure 288 (SEQ ID NO:288), Figure 290 (SEQ ID NO:290), Figure 292 (SEQ ID NO:292), Figure 294 (SEQ ID NO:294), Figure 296 (SEQ ID NO:296), Figure 298 (SEQ ID NO:298), Figure 300 (SEQ ID NO:300), Figure 302 (SEQ ID NO:302), Figure 304 (SEQ ID NO:304), Figure 306 (SEQ ID NO:306), Figure 308 (SEQ ID NO:308), Figure 310 (SEQ ID NO:310), Figure 312 (SEQ ID NO:312), Figure 314 (SEQ ID NO:314), Figure 316 (SEQ ID NO:316), Figure 318 (SEQ ID NO:318), Figure 320 (SEQ ID NO:320), Figure 322 (SEQ ID NO:322), Figure 324 (SEQ ID NO:324), Figure 326 (SEQ ID NO:326), Figure 328 (SEQ ID NO:328), Figure 330 (SEQ ID NO:330), Figure 332 (SEQ ID NO:332), Figure 334 (SEQ ID NO:334), Figure 336 (SEQ ID NO:336), Figure 338 (SEQ ID NO:338), Figure 340 (SEQ ID NO:340), Figure 342 (SEQ ID NO:342), Figure 344 (SEQ ID NO:344), Figure 346 (SEQ ID NO:346), Figure 348 (SEQ ID NO:348), Figure 350 (SEQ ID NO:350), Figure 352 (SEQ ID NO:352), Figure 354 (SEQ ID NO:354), Figure 356 (SEQ ID NO:356), Figure 358 (SEQ ID NO:358), Figure 360 (SEQ ID NO:360), Figure 362 (SEQ ID NO:362), Figure 364 (SEQ ID NO:364), Figure 366 (SEQ ID NO:366), Figure 368 (SEQ ID NO:368), Figure 370 (SEQ ID NO:370), Figure 372 (SEQ ID NO:372) and Figure 374 (SEQ ID NO:374).

2. An isolated nucleic acid molecule having at least 80% nucleic acid sequence identity to a nucleotide sequence selected from the group consisting of the nucleotide sequence shown in Figure 1 (SEQ ID NO:1), Figure 3 (SEQ ID NO:3), Figure 5 (SEQ ID NO:5), Figure 7 (SEQ ID NO:7), Figure 9 (SEQ ID NO:9), Figure 11 (SEQ ID NO:11), Figure 13 (SEQ ID NO:13), Figure 15 (SEQ ID NO:15), Figure 17 (SEQ ID NO:17), Figure 19 (SEQ ID NO:19), Figure 21 (SEQ ID NO:21), Figure 23 (SEQ ID NO:23), Figure 25 (SEQ ID NO:25), Figure 27 (SEQ ID NO:27), Figure 29 (SEQ ID NO:29), Figure 31 (SEQ ID NO:31), Figure 33 (SEQ ID NO:33), Figure 35 (SEQ ID NO:35), Figure 37 (SEQ ID NO:37), Figure 39 (SEQ ID NO:39), Figure 41 (SEQ ID NO:41), Figure 43 (SEQ ID NO:43), Figure 45 (SEQ ID NO:45), Figure 47 (SEQ ID NO:47), Figure 49 (SEQ ID NO:49), Figure 51 (SEQ ID NO:51), Figure 53 (SEQ ID NO:53), Figure 55 (SEQ ID NO:55), Figure 57 (SEQ ID NO:57), Figure 59 (SEQ ID NO:59), Figure 61 (SEQ ID NO:61), Figure 63 (SEQ ID NO:63), Figure 65 (SEQ ID NO:65), Figure 67 (SEQ ID NO:67), Figure 69 (SEQ ID NO:69), Figure 71 (SEQ ID NO:71), Figure 73 (SEQ ID NO:73), Figures 75A-75B (SEQ ID NO:75), Figure 77 (SEQ ID NO:77), Figure 79 (SEQ ID NO:79), Figure 81 (SEQ ID NO:81), Figure 83 (SEQ ID NO:83), Figure 85 (SEQ ID NO:85), Figure 87 (SEQ ID NO:87), Figure 89 (SEQ ID NO:89), Figure 91 (SEQ ID NO:91), Figure 93 (SEQ ID NO:93), Figure 95 (SEQ ID NO:95), Figure 97 (SEQ ID NO:97), Figure 99 (SEQ ID NO:99), Figure 101 (SEQ ID NO:101), Figure 103 (SEQ ID NO:103), Figure 105 (SEQ ID NO:105), Figure 107 (SEQ ID NO:107), Figure 109 (SEQ ID NO:109), Figure 111 (SEQ ID NO:111), Figure 113 (SEQ ID NO:113), Figure 115 (SEQ

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 20 249 (SEQ ID NO:249), Figure 251 (SEQ ID NO:251), Figure 253 (SEQ ID NO:253), Figure 255 (SEQ ID  
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 35 ID NO:353), Figure 355 (SEQ ID NO:355), Figure 357 (SEQ ID NO:357), Figure 359 (SEQ ID NO:359), Figure  
 361 (SEQ ID NO:361), Figure 363 (SEQ ID NO:363), Figure 365 (SEQ ID NO:365), Figure 367 (SEQ ID  
 NO:367), Figure 369 (SEQ ID NO:369), Figure 371 (SEQ ID NO:371) and Figure 373 (SEQ ID NO:373).



3. An isolated nucleic acid molecule having at least 80% nucleic acid sequence identity to a nucleotide sequence selected from the group consisting of the full-length coding sequence of the nucleotide sequence shown in Figure 1 (SEQ ID NO:1), Figure 3 (SEQ ID NO:3), Figure 5 (SEQ ID NO:5), Figure 7 (SEQ ID NO:7), Figure 9 (SEQ ID NO:9), Figure 11 (SEQ ID NO:11), Figure 13 (SEQ ID NO:13), Figure 15 (SEQ ID NO:15), Figure 17 (SEQ ID NO:17), Figure 19 (SEQ ID NO:19), Figure 21 (SEQ ID NO:21), Figure 23 (SEQ ID NO:23), Figure 25 (SEQ ID NO:25), Figure 27 (SEQ ID NO:27), Figure 29 (SEQ ID NO:29), Figure 31 (SEQ ID NO:31), Figure 33 (SEQ ID NO:33), Figure 35 (SEQ ID NO:35), Figure 37 (SEQ ID NO:37), Figure 39 (SEQ ID NO:39), Figure 41 (SEQ ID NO:41), Figure 43 (SEQ ID NO:43), Figure 45 (SEQ ID NO:45), Figure 47 (SEQ ID NO:47), Figure 49 (SEQ ID NO:49), Figure 51 (SEQ ID NO:51), Figure 53 (SEQ ID NO:53), Figure 55 (SEQ ID NO:55), Figure 57 (SEQ ID NO:57), Figure 59 (SEQ ID NO:59), Figure 61 (SEQ ID NO:61), Figure 63 (SEQ ID NO:63), Figure 65 (SEQ ID NO:65), Figure 67 (SEQ ID NO:67), Figure 69 (SEQ ID NO:69), Figure 71 (SEQ ID NO:71), Figure 73 (SEQ ID NO:73), Figures 75A-75B (SEQ ID NO:75), Figure 77 (SEQ ID NO:77), Figure 79 (SEQ ID NO:79), Figure 81 (SEQ ID NO:81), Figure 83 (SEQ ID NO:83), Figure 85 (SEQ ID NO:85), Figure 87 (SEQ ID NO:87), Figure 89 (SEQ ID NO:89), Figure 91 (SEQ ID NO:91), Figure 93 (SEQ ID NO:93), Figure 95 (SEQ ID NO:95), Figure 97 (SEQ ID NO:97), Figure 99 (SEQ ID NO:99), Figure 101 (SEQ ID NO:101), Figure 103 (SEQ ID NO:103), Figure 105 (SEQ ID NO:105), Figure 107 (SEQ ID NO:107), Figure 109 (SEQ ID NO:109), Figure 111 (SEQ ID NO:111), Figure 113 (SEQ ID NO:113), Figure 115 (SEQ ID NO:115), Figure 117 (SEQ ID NO:117), Figure 119 (SEQ ID NO:119), Figure 121 (SEQ ID NO:121), Figure 123 (SEQ ID NO:123), Figure 125 (SEQ ID NO:125), Figure 127 (SEQ ID NO:127), Figure 129 (SEQ ID NO:129), Figure 131 (SEQ ID NO:131), Figure 133 (SEQ ID NO:133), Figure 135 (SEQ ID NO:135), Figure 137 (SEQ ID NO:137), Figure 139 (SEQ ID NO:139), Figure 141 (SEQ ID NO:141), Figure 143 (SEQ ID NO:143), Figure 145 (SEQ ID NO:145), Figure 147 (SEQ ID NO:147), Figure 149 (SEQ ID NO:149), Figure 151 (SEQ ID NO:151), Figure 153 (SEQ ID NO:153), Figure 155 (SEQ ID NO:155), Figure 157 (SEQ ID NO:157), Figure 159 (SEQ ID NO:159), Figure 161 (SEQ ID NO:161), Figure 163 (SEQ ID NO:163), Figure 165 (SEQ ID NO:165), Figure 167 (SEQ ID NO:167), Figure 169 (SEQ ID NO:169), Figure 171 (SEQ ID NO:171), Figure 173 (SEQ ID NO:173), Figure 175 (SEQ ID NO:175), Figure 177 (SEQ ID NO:177), Figure 179 (SEQ ID NO:179), Figure 181 (SEQ ID NO:181), Figure 183 (SEQ ID NO:183), Figure 185 (SEQ ID NO:185), Figure 187 (SEQ ID NO:187), Figure 189 (SEQ ID NO:189), Figure 191 (SEQ ID NO:191), Figure 193 (SEQ ID NO:193), Figure 195 (SEQ ID NO:195), Figure 197 (SEQ ID NO:197), Figure 199 (SEQ ID NO:199), Figure 201 (SEQ ID NO:201), Figure 203 (SEQ ID NO:203), Figure 205 (SEQ ID NO:205), Figure 207 (SEQ ID NO:207), Figure 209 (SEQ ID NO:209), Figure 211 (SEQ ID NO:211), Figure 213 (SEQ ID NO:213), Figure 215 (SEQ ID NO:215), Figure 217 (SEQ ID NO:217), Figure 219 (SEQ ID NO:219), Figure 221 (SEQ ID NO:221), Figure 223 (SEQ ID NO:223), Figure 225 (SEQ ID NO:225), Figure 227 (SEQ ID NO:227), Figure 229 (SEQ ID NO:229), Figure 231 (SEQ ID NO:231), Figure 233 (SEQ ID NO:233), Figure 235 (SEQ ID NO:235), Figure 237 (SEQ ID NO:237), Figure 239 (SEQ ID NO:239), Figure 241 (SEQ ID NO:241), Figure 243 (SEQ ID NO:243), Figure 245 (SEQ ID NO:245), Figure 247 (SEQ ID NO:247), Figure 249 (SEQ ID NO:249), Figure 251 (SEQ ID NO:251), Figure

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4. An isolated nucleic acid molecule having at least 80% nucleic acid sequence identity to the full-length coding sequence of the DNA deposited under any ATCC accession number shown in Table 7.

5. A vector comprising the nucleic acid of Claim 1.

6. A host cell comprising the vector of Claim 5.

7. The host cell of Claim 6, wherein said cell is a CHO cell.

8. The host cell of Claim 6, wherein said cell is an *E. coli*.

9. The host cell of Claim 6, wherein said cell is a yeast cell.

10. A process for producing a PRO polypeptide comprising culturing the host cell of Claim 6 under conditions suitable for expression of said PRO polypeptide and recovering said PRO polypeptide from the cell culture.

11. An isolated polypeptide having at least 80% amino acid sequence identity to an amino acid sequence selected from the group consisting of the amino acid sequence shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160), Figure 162 (SEQ ID NO:162), Figure 164 (SEQ ID NO:164), Figure 166 (SEQ ID NO:166), Figure 168 (SEQ ID NO:168), Figure 170 (SEQ ID NO:170), Figure 172 (SEQ ID NO:172), Figure 174 (SEQ ID NO:174), Figure 176 (SEQ ID NO:176), Figure 178 (SEQ ID NO:178), Figure 180 (SEQ ID NO:180), Figure 182 (SEQ ID NO:182), Figure 184 (SEQ ID NO:184), Figure 186 (SEQ ID NO:186), Figure 188 (SEQ ID NO:188), Figure 190 (SEQ ID NO:190), Figure 192 (SEQ ID NO:192), Figure 194 (SEQ ID NO:194), Figure 196 (SEQ ID NO:196), Figure 198 (SEQ ID NO:198), Figure 200 (SEQ ID NO:200), Figure 202 (SEQ ID NO:202), Figure 204 (SEQ ID NO:204), Figure 206 (SEQ ID NO:206), Figure 208 (SEQ ID NO:208), Figure 210 (SEQ ID NO:210), Figure 212 (SEQ ID NO:212), Figure 214 (SEQ ID NO:214), Figure 216 (SEQ ID NO:216), Figure 218 (SEQ ID NO:218), Figure 220 (SEQ ID NO:220), Figure 222 (SEQ ID NO:222), Figure 224 (SEQ ID NO:224), Figure 226 (SEQ ID NO:226), Figure 228 (SEQ ID NO:228), Figure 230 (SEQ ID NO:230), Figure 232 (SEQ ID NO:232), Figure 234 (SEQ ID NO:234), Figure 236 (SEQ ID NO:236), Figure 238 (SEQ ID NO:238), Figure 240 (SEQ ID NO:240), Figure 242 (SEQ ID NO:242), Figure 244 (SEQ ID NO:244), Figure 246 (SEQ ID NO:246), Figure 248 (SEQ ID NO:248), Figure 250 (SEQ ID NO:250), Figure 252 (SEQ ID NO:252), Figure 254 (SEQ ID NO:254), Figure 256 (SEQ ID

NO:256), Figure 258 (SEQ ID NO:258), Figure 260 (SEQ ID NO:260), Figure 262 (SEQ ID NO:262), Figure 264 (SEQ ID NO:264), Figure 266 (SEQ ID NO:266), Figure 268 (SEQ ID NO:268), Figure 270 (SEQ ID NO:270), Figure 272 (SEQ ID NO:272), Figure 274 (SEQ ID NO:274), Figure 276 (SEQ ID NO:276), Figure 278 (SEQ ID NO:278), Figure 280 (SEQ ID NO:280), Figure 282 (SEQ ID NO:282), Figure 284 (SEQ ID NO:284), Figure 286 (SEQ ID NO:286), Figure 288 (SEQ ID NO:288), Figure 290 (SEQ ID NO:290), Figure 292 (SEQ ID NO:292), Figure 294 (SEQ ID NO:294), Figure 296 (SEQ ID NO:296), Figure 298 (SEQ ID NO:298), Figure 300 (SEQ ID NO:300), Figure 302 (SEQ ID NO:302), Figure 304 (SEQ ID NO:304), Figure 306 (SEQ ID NO:306), Figure 308 (SEQ ID NO:308), Figure 310 (SEQ ID NO:310), Figure 312 (SEQ ID NO:312), Figure 314 (SEQ ID NO:314), Figure 316 (SEQ ID NO:316), Figure 318 (SEQ ID NO:318), Figure 320 (SEQ ID NO:320), Figure 322 (SEQ ID NO:322), Figure 324 (SEQ ID NO:324), Figure 326 (SEQ ID NO:326), Figure 328 (SEQ ID NO:328), Figure 330 (SEQ ID NO:330), Figure 332 (SEQ ID NO:332), Figure 334 (SEQ ID NO:334), Figure 336 (SEQ ID NO:336), Figure 338 (SEQ ID NO:338), Figure 340 (SEQ ID NO:340), Figure 342 (SEQ ID NO:342), Figure 344 (SEQ ID NO:344), Figure 346 (SEQ ID NO:346), Figure 348 (SEQ ID NO:348), Figure 350 (SEQ ID NO:350), Figure 352 (SEQ ID NO:352), Figure 354 (SEQ ID NO:354), Figure 356 (SEQ ID NO:356), Figure 358 (SEQ ID NO:358), Figure 360 (SEQ ID NO:360), Figure 362 (SEQ ID NO:362), Figure 364 (SEQ ID NO:364), Figure 366 (SEQ ID NO:366), Figure 368 (SEQ ID NO:368), Figure 370 (SEQ ID NO:370), Figure 372 (SEQ ID NO:372) and Figure 374 (SEQ ID NO:374).

12. An isolated polypeptide having at least 80% amino acid sequence identity to an amino acid sequence encoded by the full-length coding sequence of the DNA deposited under any ATCC accession number shown in Table 7.

13. A chimeric molecule comprising a polypeptide according to Claim 11 fused to a heterologous amino acid sequence.

14. The chimeric molecule of Claim 13, wherein said heterologous amino acid sequence is an epitope tag sequence.

15. The chimeric molecule of Claim 13, wherein said heterologous amino acid sequence is a Fc region of an immunoglobulin.

16. An antibody which specifically binds to a polypeptide according to Claim 11.

17. The antibody of Claim 16, wherein said antibody is a monoclonal antibody, a humanized antibody or a single-chain antibody.

18. An isolated nucleic acid molecule having at least 80% nucleic acid sequence identity to:

(a) a nucleotide sequence encoding the polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160), Figure 162 (SEQ ID NO:162), Figure 164 (SEQ ID NO:164), Figure 166 (SEQ ID NO:166), Figure 168 (SEQ ID NO:168), Figure 170 (SEQ ID NO:170), Figure 172 (SEQ ID NO:172), Figure 174 (SEQ ID NO:174), Figure 176 (SEQ ID NO:176), Figure 178 (SEQ ID NO:178), Figure 180 (SEQ ID NO:180), Figure 182 (SEQ ID NO:182), Figure 184 (SEQ ID NO:184), Figure 186 (SEQ ID NO:186), Figure 188 (SEQ ID NO:188), Figure 190 (SEQ ID NO:190), Figure 192 (SEQ ID NO:192), Figure 194 (SEQ ID NO:194), Figure 196 (SEQ ID NO:196), Figure 198 (SEQ ID NO:198), Figure 200 (SEQ ID NO:200), Figure 202 (SEQ ID NO:202), Figure 204 (SEQ ID NO:204), Figure 206 (SEQ ID NO:206), Figure 208 (SEQ ID NO:208), Figure 210 (SEQ ID NO:210), Figure 212 (SEQ ID NO:212), Figure 214 (SEQ ID NO:214), Figure 216 (SEQ ID NO:216), Figure 218 (SEQ ID NO:218), Figure 220 (SEQ ID NO:220), Figure 222 (SEQ ID NO:222), Figure 224 (SEQ ID NO:224), Figure 226 (SEQ ID NO:226), Figure 228 (SEQ ID NO:228), Figure 230 (SEQ ID NO:230), Figure 232 (SEQ ID NO:232), Figure 234 (SEQ ID NO:234), Figure 236 (SEQ ID NO:236), Figure 238 (SEQ ID NO:238), Figure 240 (SEQ ID NO:240), Figure 242 (SEQ ID NO:242), Figure 244 (SEQ ID NO:244), Figure 246 (SEQ ID NO:246), Figure 248 (SEQ ID NO:248), Figure 250 (SEQ ID NO:250), Figure 252 (SEQ ID NO:252), Figure 254 (SEQ ID NO:254), Figure 256 (SEQ ID NO:256), Figure 258 (SEQ ID NO:258), Figure 260 (SEQ ID NO:260), Figure 262 (SEQ ID NO:262), Figure 264 (SEQ ID NO:264), Figure 266 (SEQ ID NO:266), Figure 268 (SEQ ID NO:268), Figure 270 (SEQ ID NO:270), Figure 272 (SEQ ID NO:272), Figure 274 (SEQ ID NO:274), Figure 276 (SEQ ID NO:276), Figure 278 (SEQ ID NO:278), Figure 280 (SEQ ID NO:280), Figure 282 (SEQ ID NO:282), Figure 284 (SEQ ID NO:284), Figure 286 (SEQ ID NO:286), Figure 288 (SEQ ID NO:288), Figure 290 (SEQ ID NO:290), Figure 292 (SEQ ID NO:292), Figure 294 (SEQ ID NO:294), Figure 296 (SEQ ID NO:296), Figure 298 (SEQ ID NO:298), Figure 300 (SEQ ID NO:300).

NO:264), Figure 266 (SEQ ID NO:266), Figure 268 (SEQ ID NO:268), Figure 270 (SEQ ID NO:270), Figure 272 (SEQ ID NO:272), Figure 274 (SEQ ID NO:274), Figure 276 (SEQ ID NO:276), Figure 278 (SEQ ID NO:278), Figure 280 (SEQ ID NO:280), Figure 282 (SEQ ID NO:282), Figure 284 (SEQ ID NO:284), Figure 286 (SEQ ID NO:286), Figure 288 (SEQ ID NO:288), Figure 290 (SEQ ID NO:290), Figure 292 (SEQ ID NO:292), Figure 294 (SEQ ID NO:294), Figure 296 (SEQ ID NO:296), Figure 298 (SEQ ID NO:298), Figure 300 (SEQ ID NO:300), Figure 302 (SEQ ID NO:302), Figure 304 (SEQ ID NO:304), Figure 306 (SEQ ID NO:306), Figure 308 (SEQ ID NO:308), Figure 310 (SEQ ID NO:310), Figure 312 (SEQ ID NO:312), Figure 314 (SEQ ID NO:314), Figure 316 (SEQ ID NO:316), Figure 318 (SEQ ID NO:318), Figure 320 (SEQ ID NO:320), Figure 322 (SEQ ID NO:322), Figure 324 (SEQ ID NO:324), Figure 326 (SEQ ID NO:326), Figure 328 (SEQ ID NO:328), Figure 330 (SEQ ID NO:330), Figure 332 (SEQ ID NO:332), Figure 334 (SEQ ID NO:334), Figure 336 (SEQ ID NO:336), Figure 338 (SEQ ID NO:338), Figure 340 (SEQ ID NO:340), Figure 342 (SEQ ID NO:342), Figure 344 (SEQ ID NO:344), Figure 346 (SEQ ID NO:346), Figure 348 (SEQ ID NO:348), Figure 350 (SEQ ID NO:350), Figure 352 (SEQ ID NO:352), Figure 354 (SEQ ID NO:354), Figure 356 (SEQ ID NO:356), Figure 358 (SEQ ID NO:358), Figure 360 (SEQ ID NO:360), Figure 362 (SEQ ID NO:362), Figure 364 (SEQ ID NO:364), Figure 366 (SEQ ID NO:366), Figure 368 (SEQ ID NO:368), Figure 370 (SEQ ID NO:370), Figure 372 (SEQ ID NO:372) or Figure 374 (SEQ ID NO:374), lacking its associated signal peptide;

(b) a nucleotide sequence encoding an extracellular domain of the polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure

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(c) a nucleotide sequence encoding an extracellular domain of the polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18

(SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160), Figure 162 (SEQ ID NO:162), Figure 164 (SEQ ID NO:164), Figure 166 (SEQ ID NO:166), Figure 168 (SEQ ID NO:168), Figure 170 (SEQ ID NO:170), Figure 172 (SEQ ID NO:172), Figure 174 (SEQ ID NO:174), Figure 176 (SEQ ID NO:176), Figure 178 (SEQ ID NO:178), Figure 180 (SEQ ID NO:180), Figure 182 (SEQ ID NO:182), Figure 184 (SEQ ID NO:184), Figure 186 (SEQ ID NO:186), Figure 188 (SEQ ID NO:188), Figure 190 (SEQ ID NO:190), Figure 192 (SEQ ID NO:192), Figure 194 (SEQ ID NO:194), Figure 196 (SEQ ID NO:196), Figure 198 (SEQ ID NO:198), Figure 200 (SEQ ID NO:200), Figure 202 (SEQ ID NO:202), Figure 204 (SEQ ID NO:204), Figure 206 (SEQ ID NO:206), Figure 208 (SEQ ID NO:208), Figure 210 (SEQ ID NO:210), Figure 212 (SEQ ID NO:212), Figure 214 (SEQ ID NO:214), Figure 216 (SEQ ID NO:216), Figure 218 (SEQ ID NO:218), Figure 220 (SEQ ID NO:220), Figure 222 (SEQ ID NO:222), Figure 224 (SEQ ID NO:224), Figure 226 (SEQ ID NO:226), Figure 228 (SEQ ID NO:228), Figure 230 (SEQ ID NO:230), Figure 232 (SEQ ID NO:232), Figure 234 (SEQ ID NO:234), Figure 236 (SEQ ID NO:236), Figure 238 (SEQ ID NO:238), Figure 240 (SEQ ID NO:240), Figure 242 (SEQ ID NO:242), Figure 244 (SEQ ID NO:244), Figure 246 (SEQ ID NO:246), Figure 248 (SEQ ID NO:248), Figure 250 (SEQ ID NO:250), Figure 252 (SEQ ID NO:252), Figure 254 (SEQ ID NO:254), Figure 256 (SEQ ID NO:256), Figure 258 (SEQ ID NO:258), Figure 260 (SEQ ID NO:260), Figure 262 (SEQ ID NO:262), Figure 264 (SEQ ID NO:264), Figure 266 (SEQ ID NO:266), Figure 268 (SEQ ID NO:268), Figure 270 (SEQ ID NO:270), Figure 272 (SEQ ID NO:272), Figure 274 (SEQ ID NO:274), Figure 276 (SEQ ID NO:276), Figure 278 (SEQ ID NO:278), Figure 280 (SEQ ID NO:280), Figure 282 (SEQ ID NO:282), Figure



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19. An isolated polypeptide having at least 80% amino acid sequence identity to:

(a) an amino acid sequence of the polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID

NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160), Figure 162 (SEQ ID NO:162), Figure 164 (SEQ ID NO:164), Figure 166 (SEQ ID NO:166), Figure 168 (SEQ ID NO:168), Figure 170 (SEQ ID NO:170), Figure 172 (SEQ ID NO:172), Figure 174 (SEQ ID NO:174), Figure 176 (SEQ ID NO:176), Figure 178 (SEQ ID NO:178), Figure 180 (SEQ ID NO:180), Figure 182 (SEQ ID NO:182), Figure 184 (SEQ ID NO:184), Figure 186 (SEQ ID NO:186), Figure 188 (SEQ ID NO:188), Figure 190 (SEQ ID NO:190), Figure 192 (SEQ ID NO:192), Figure 194 (SEQ ID NO:194), Figure 196 (SEQ ID NO:196), Figure 198 (SEQ ID NO:198), Figure 200 (SEQ ID NO:200), Figure 202 (SEQ ID NO:202), Figure 204 (SEQ ID NO:204), Figure 206 (SEQ ID NO:206), Figure 208 (SEQ ID NO:208), Figure 210 (SEQ ID NO:210), Figure 212 (SEQ ID NO:212), Figure 214 (SEQ ID NO:214), Figure 216 (SEQ ID NO:216), Figure 218 (SEQ ID NO:218), Figure 220 (SEQ ID NO:220), Figure 222 (SEQ ID NO:222), Figure 224 (SEQ ID NO:224), Figure 226 (SEQ ID NO:226), Figure 228 (SEQ ID NO:228), Figure 230 (SEQ ID NO:230), Figure 232 (SEQ ID NO:232), Figure 234 (SEQ ID NO:234), Figure 236 (SEQ ID NO:236), Figure 238 (SEQ ID NO:238), Figure 240 (SEQ ID NO:240), Figure 242 (SEQ ID NO:242), Figure 244 (SEQ ID NO:244), Figure 246 (SEQ ID NO:246), Figure 248 (SEQ ID NO:248), Figure 250 (SEQ ID NO:250), Figure 252 (SEQ ID NO:252), Figure 254 (SEQ ID NO:254), Figure 256 (SEQ ID NO:256), Figure 258 (SEQ ID NO:258), Figure 260 (SEQ ID NO:260), Figure 262 (SEQ ID NO:262), Figure 264 (SEQ ID NO:264), Figure 266 (SEQ ID NO:266), Figure 268 (SEQ ID NO:268), Figure 270 (SEQ ID NO:270), Figure 272 (SEQ ID NO:272), Figure 274 (SEQ ID NO:274), Figure 276 (SEQ ID NO:276), Figure 278 (SEQ ID NO:278), Figure 280 (SEQ ID NO:280), Figure 282 (SEQ ID NO:282), Figure 284 (SEQ ID NO:284), Figure 286 (SEQ ID NO:286), Figure 288 (SEQ ID NO:288), Figure 290 (SEQ ID NO:290), Figure 292 (SEQ ID NO:292), Figure 294 (SEQ ID NO:294), Figure 296 (SEQ ID NO:296), Figure 298 (SEQ ID NO:298), Figure 300 (SEQ ID NO:300), Figure 302 (SEQ ID NO:302), Figure 304 (SEQ ID NO:304), Figure 306 (SEQ ID NO:306), Figure 308 (SEQ ID NO:308), Figure 310 (SEQ ID NO:310), Figure 312 (SEQ ID NO:312), Figure 314 (SEQ ID NO:314), Figure 316 (SEQ ID NO:316), Figure 318 (SEQ ID NO:318), Figure 320 (SEQ ID NO:320), Figure 322 (SEQ ID NO:322), Figure 324 (SEQ ID NO:324), Figure 326 (SEQ ID NO:326), Figure 328 (SEQ ID NO:328), Figure 330 (SEQ ID NO:330), Figure 332 (SEQ ID NO:332), Figure 334 (SEQ ID NO:334), Figure 336 (SEQ ID NO:336), Figure 338 (SEQ ID NO:338), Figure 340 (SEQ ID NO:340), Figure 342 (SEQ ID NO:342), Figure 344 (SEQ ID NO:344), Figure 346 (SEQ ID NO:346), Figure 348 (SEQ ID NO:348), Figure 350 (SEQ ID NO:350), Figure 352 (SEQ ID NO:352), Figure 354 (SEQ ID NO:354), Figure 356 (SEQ ID NO:356), Figure 358 (SEQ ID NO:358), Figure 360 (SEQ ID NO:360), Figure 362 (SEQ ID NO:362), Figure 364 (SEQ ID NO:364), Figure 366 (SEQ ID NO:366), Figure 368 (SEQ ID NO:368), Figure 370 (SEQ ID NO:370), Figure 372 (SEQ ID NO:372) or Figure 374 (SEQ ID NO:374), lacking its associated signal peptide;

(b) an amino acid sequence of an extracellular domain of the polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26

(SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160), Figure 162 (SEQ ID NO:162), Figure 164 (SEQ ID NO:164), Figure 166 (SEQ ID NO:166), Figure 168 (SEQ ID NO:168), Figure 170 (SEQ ID NO:170), Figure 172 (SEQ ID NO:172), Figure 174 (SEQ ID NO:174), Figure 176 (SEQ ID NO:176), Figure 178 (SEQ ID NO:178), Figure 180 (SEQ ID NO:180), Figure 182 (SEQ ID NO:182), Figure 184 (SEQ ID NO:184), Figure 186 (SEQ ID NO:186), Figure 188 (SEQ ID NO:188), Figure 190 (SEQ ID NO:190), Figure 192 (SEQ ID NO:192), Figure 194 (SEQ ID NO:194), Figure 196 (SEQ ID NO:196), Figure 198 (SEQ ID NO:198), Figure 200 (SEQ ID NO:200), Figure 202 (SEQ ID NO:202), Figure 204 (SEQ ID NO:204), Figure 206 (SEQ ID NO:206), Figure 208 (SEQ ID NO:208), Figure 210 (SEQ ID NO:210), Figure 212 (SEQ ID NO:212), Figure 214 (SEQ ID NO:214), Figure 216 (SEQ ID NO:216), Figure 218 (SEQ ID NO:218), Figure 220 (SEQ ID NO:220), Figure 222 (SEQ ID NO:222), Figure 224 (SEQ ID NO:224), Figure 226 (SEQ ID NO:226), Figure 228 (SEQ ID NO:228), Figure 230 (SEQ ID NO:230), Figure 232 (SEQ ID NO:232), Figure 234 (SEQ ID NO:234), Figure 236 (SEQ ID NO:236), Figure 238 (SEQ ID NO:238), Figure 240 (SEQ ID NO:240), Figure 242 (SEQ ID NO:242), Figure 244 (SEQ ID NO:244), Figure 246 (SEQ ID NO:246), Figure 248 (SEQ ID NO:248), Figure 250 (SEQ ID NO:250), Figure 252 (SEQ ID NO:252), Figure 254 (SEQ ID NO:254), Figure 256 (SEQ ID NO:256), Figure 258 (SEQ ID NO:258), Figure 260 (SEQ ID NO:260), Figure 262 (SEQ ID NO:262), Figure 264 (SEQ ID NO:264), Figure 266 (SEQ ID NO:266), Figure 268 (SEQ ID NO:268), Figure 270 (SEQ ID NO:270), Figure 272 (SEQ ID NO:272), Figure 274 (SEQ ID NO:274), Figure 276 (SEQ ID NO:276), Figure 278 (SEQ ID NO:278), Figure 280 (SEQ ID NO:280), Figure 282 (SEQ ID NO:282), Figure 284 (SEQ ID NO:284), Figure 286 (SEQ ID NO:286), Figure 288 (SEQ ID NO:288), Figure 290 (SEQ ID NO:290), Figure

292 (SEQ ID NO:292), Figure 294 (SEQ ID NO:294), Figure 296 (SEQ ID NO:296), Figure 298 (SEQ ID NO:298), Figure 300 (SEQ ID NO:300), Figure 302 (SEQ ID NO:302), Figure 304 (SEQ ID NO:304), Figure 306 (SEQ ID NO:306), Figure 308 (SEQ ID NO:308), Figure 310 (SEQ ID NO:310), Figure 312 (SEQ ID NO:312), Figure 314 (SEQ ID NO:314), Figure 316 (SEQ ID NO:316), Figure 318 (SEQ ID NO:318), Figure 320 (SEQ ID NO:320), Figure 322 (SEQ ID NO:322), Figure 324 (SEQ ID NO:324), Figure 326 (SEQ ID NO:326), Figure 328 (SEQ ID NO:328), Figure 330 (SEQ ID NO:330), Figure 332 (SEQ ID NO:332), Figure 334 (SEQ ID NO:334), Figure 336 (SEQ ID NO:336), Figure 338 (SEQ ID NO:338), Figure 340 (SEQ ID NO:340), Figure 342 (SEQ ID NO:342), Figure 344 (SEQ ID NO:344), Figure 346 (SEQ ID NO:346), Figure 348 (SEQ ID NO:348), Figure 350 (SEQ ID NO:350), Figure 352 (SEQ ID NO:352), Figure 354 (SEQ ID NO:354), Figure 356 (SEQ ID NO:356), Figure 358 (SEQ ID NO:358), Figure 360 (SEQ ID NO:360), Figure 362 (SEQ ID NO:362), Figure 364 (SEQ ID NO:364), Figure 366 (SEQ ID NO:366), Figure 368 (SEQ ID NO:368), Figure 370 (SEQ ID NO:370), Figure 372 (SEQ ID NO:372) or Figure 374 (SEQ ID NO:374), with its associated signal peptide; or

(c) an amino acid sequence of an extracellular domain of the polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160), Figure 162 (SEQ ID NO:162), Figure 164 (SEQ ID NO:164), Figure 166 (SEQ ID NO:166), Figure 168 (SEQ ID NO:168), Figure 170 (SEQ ID NO:170), Figure 172 (SEQ ID

NO:172), Figure 174 (SEQ ID NO:174), Figure 176 (SEQ ID NO:176), Figure 178 (SEQ ID NO:178), Figure  
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 348 (SEQ ID NO:348), Figure 350 (SEQ ID NO:350), Figure 352 (SEQ ID NO:352), Figure 354 (SEQ ID  
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 362 (SEQ ID NO:362), Figure 364 (SEQ ID NO:364), Figure 366 (SEQ ID NO:366), Figure 368 (SEQ ID  
 NO:368), Figure 370 (SEQ ID NO:370), Figure 372 (SEQ ID NO:372) or Figure 374 (SEQ ID NO:374), lacking  
 30 its associated signal peptide.

20. A method for treating a cardiovascular, endothelial or angiogenic disorder in a mammal  
 comprising administering to the mammal a therapeutically effective amount of a polypeptide shown in Figure 2  
 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ  
 35 ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18  
 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure  
 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32),

Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160), Figure 162 (SEQ ID NO:162), Figure 164 (SEQ ID NO:164), Figure 166 (SEQ ID NO:166), Figure 168 (SEQ ID NO:168), Figure 170 (SEQ ID NO:170), Figure 172 (SEQ ID NO:172), Figure 174 (SEQ ID NO:174), Figure 176 (SEQ ID NO:176), Figure 178 (SEQ ID NO:178), Figure 180 (SEQ ID NO:180), Figure 182 (SEQ ID NO:182), Figure 184 (SEQ ID NO:184), Figure 186 (SEQ ID NO:186), Figure 188 (SEQ ID NO:188), Figure 190 (SEQ ID NO:190), Figure 192 (SEQ ID NO:192), Figure 194 (SEQ ID NO:194), Figure 196 (SEQ ID NO:196), Figure 198 (SEQ ID NO:198), Figure 200 (SEQ ID NO:200), Figure 202 (SEQ ID NO:202), Figure 204 (SEQ ID NO:204), Figure 206 (SEQ ID NO:206), Figure 208 (SEQ ID NO:208), Figure 210 (SEQ ID NO:210), Figure 212 (SEQ ID NO:212), Figure 214 (SEQ ID NO:214), Figure 216 (SEQ ID NO:216), Figure 218 (SEQ ID NO:218), Figure 220 (SEQ ID NO:220), Figure 222 (SEQ ID NO:222), Figure 224 (SEQ ID NO:224), Figure 226 (SEQ ID NO:226), Figure 228 (SEQ ID NO:228), Figure 230 (SEQ ID NO:230), Figure 232 (SEQ ID NO:232), Figure 234 (SEQ ID NO:234), Figure 236 (SEQ ID NO:236), Figure 238 (SEQ ID NO:238), Figure 240 (SEQ ID NO:240), Figure 242 (SEQ ID NO:242), Figure 244 (SEQ ID NO:244), Figure 246 (SEQ ID NO:246), Figure 248 (SEQ ID NO:248), Figure 250 (SEQ ID NO:250), Figure 252 (SEQ ID NO:252), Figure 254 (SEQ ID NO:254), Figure 256 (SEQ ID NO:256), Figure 258 (SEQ ID NO:258), Figure 260 (SEQ ID NO:260), Figure 262 (SEQ ID NO:262), Figure 264 (SEQ ID NO:264), Figure 266 (SEQ ID NO:266), Figure 268 (SEQ ID NO:268), Figure 270 (SEQ ID NO:270), Figure 272 (SEQ ID NO:272), Figure 274 (SEQ ID NO:274), Figure 276 (SEQ ID NO:276), Figure 278 (SEQ ID NO:278), Figure 280 (SEQ ID NO:280), Figure 282 (SEQ ID NO:282), Figure 284 (SEQ ID NO:284), Figure 286 (SEQ ID NO:286), Figure 288 (SEQ ID NO:288), Figure 290 (SEQ ID NO:290), Figure 292 (SEQ ID NO:292), Figure 294 (SEQ ID NO:294), Figure 296 (SEQ ID NO:296), Figure

298 (SEQ ID NO:298), Figure 300 (SEQ ID NO:300), Figure 302 (SEQ ID NO:302), Figure 304 (SEQ ID NO:304), Figure 306 (SEQ ID NO:306), Figure 308 (SEQ ID NO:308), Figure 310 (SEQ ID NO:310), Figure 312 (SEQ ID NO:312), Figure 314 (SEQ ID NO:314), Figure 316 (SEQ ID NO:316), Figure 318 (SEQ ID NO:318), Figure 320 (SEQ ID NO:320), Figure 322 (SEQ ID NO:322), Figure 324 (SEQ ID NO:324), Figure 326 (SEQ ID NO:326), Figure 328 (SEQ ID NO:328), Figure 330 (SEQ ID NO:330), Figure 332 (SEQ ID NO:332), Figure 334 (SEQ ID NO:334), Figure 336 (SEQ ID NO:336), Figure 338 (SEQ ID NO:338), Figure 340 (SEQ ID NO:340), Figure 342 (SEQ ID NO:342), Figure 344 (SEQ ID NO:344), Figure 346 (SEQ ID NO:346), Figure 348 (SEQ ID NO:348), Figure 350 (SEQ ID NO:350), Figure 352 (SEQ ID NO:352), Figure 354 (SEQ ID NO:354), Figure 356 (SEQ ID NO:356), Figure 358 (SEQ ID NO:358), Figure 360 (SEQ ID NO:360), Figure 362 (SEQ ID NO:362), Figure 364 (SEQ ID NO:364), Figure 366 (SEQ ID NO:366), Figure 368 (SEQ ID NO:368), Figure 370 (SEQ ID NO:370), Figure 372 (SEQ ID NO:372) or Figure 374 (SEQ ID NO:374), or agonist or antagonist thereof.

21. The method according to Claim 20, wherein the mammal is human.

22. The method of Claim 21, wherein the human has suffered myocardial infarction.

23. The method of Claim 21, wherein the human has cardiac hypertrophy, trauma, a cancer, or age-related macular degeneration.

24. The method of Claim 23, wherein the cardiac hypertrophy is characterized by the presence of an elevated level of  $\text{PGF}_{2\alpha}$ .

25. The method of Claim 20, wherein the polypeptide is administered together with a cardiovascular, endothelial or angiogenic agent.

26. The method of Claim 23, wherein the polypeptide is administered following primary angioplasty.

27. The method of Claim 20, wherein the cardiovascular, endothelial or angiogenic disorder is cancer.

28. The method of Claim 27, wherein the polypeptide is administered in combination with a chemotherapeutic agent, a growth inhibitory agent or a cytotoxic agent.

29. The method of Claim 20, wherein said agonist is an antibody to said polypeptide.

30. The method of Claim 20, wherein said antagonist is an antibody to said polypeptide.

31. A method for treating a cardiovascular, endothelial or angiogenic disorder in a mammal comprising administering to the mammal a nucleic acid molecule that encodes a polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160), Figure 162 (SEQ ID NO:162), Figure 164 (SEQ ID NO:164), Figure 166 (SEQ ID NO:166), Figure 168 (SEQ ID NO:168), Figure 170 (SEQ ID NO:170), Figure 172 (SEQ ID NO:172), Figure 174 (SEQ ID NO:174), Figure 176 (SEQ ID NO:176), Figure 178 (SEQ ID NO:178), Figure 180 (SEQ ID NO:180), Figure 182 (SEQ ID NO:182), Figure 184 (SEQ ID NO:184), Figure 186 (SEQ ID NO:186), Figure 188 (SEQ ID NO:188), Figure 190 (SEQ ID NO:190), Figure 192 (SEQ ID NO:192), Figure 194 (SEQ ID NO:194), Figure 196 (SEQ ID NO:196), Figure 198 (SEQ ID NO:198), Figure 200 (SEQ ID NO:200), Figure 202 (SEQ ID NO:202), Figure 204 (SEQ ID NO:204), Figure 206 (SEQ ID NO:206), Figure 208 (SEQ ID NO:208), Figure 210 (SEQ ID NO:210), Figure 212 (SEQ ID NO:212), Figure 214 (SEQ ID NO:214), Figure 216 (SEQ ID NO:216), Figure 218 (SEQ ID NO:218), Figure 220 (SEQ ID NO:220), Figure 222 (SEQ ID NO:222), Figure 224 (SEQ ID NO:224), Figure 226 (SEQ ID NO:226), Figure 228 (SEQ ID NO:228), Figure 230 (SEQ ID NO:230), Figure 232 (SEQ ID NO:232), Figure 234 (SEQ ID NO:234), Figure 236 (SEQ ID NO:236), Figure 238 (SEQ ID NO:238), Figure 240 (SEQ ID NO:240), Figure 242 (SEQ ID NO:242), Figure 244 (SEQ ID NO:244), Figure 246 (SEQ ID NO:246), Figure 248 (SEQ ID NO:248), Figure 250 (SEQ ID NO:250), Figure 252 (SEQ ID NO:252), Figure 254 (SEQ ID NO:254), Figure



256 (SEQ ID NO:256), Figure 258 (SEQ ID NO:258), Figure 260 (SEQ ID NO:260), Figure 262 (SEQ ID NO:262), Figure 264 (SEQ ID NO:264), Figure 266 (SEQ ID NO:266), Figure 268 (SEQ ID NO:268), Figure 270 (SEQ ID NO:270), Figure 272 (SEQ ID NO:272), Figure 274 (SEQ ID NO:274), Figure 276 (SEQ ID NO:276), Figure 278 (SEQ ID NO:278), Figure 280 (SEQ ID NO:280), Figure 282 (SEQ ID NO:282), Figure 284 (SEQ ID NO:284), Figure 286 (SEQ ID NO:286), Figure 288 (SEQ ID NO:288), Figure 290 (SEQ ID NO:290), Figure 292 (SEQ ID NO:292), Figure 294 (SEQ ID NO:294), Figure 296 (SEQ ID NO:296), Figure 298 (SEQ ID NO:298), Figure 300 (SEQ ID NO:300), Figure 302 (SEQ ID NO:302), Figure 304 (SEQ ID NO:304), Figure 306 (SEQ ID NO:306), Figure 308 (SEQ ID NO:308), Figure 310 (SEQ ID NO:310), Figure 312 (SEQ ID NO:312), Figure 314 (SEQ ID NO:314), Figure 316 (SEQ ID NO:316), Figure 318 (SEQ ID NO:318), Figure 320 (SEQ ID NO:320), Figure 322 (SEQ ID NO:322), Figure 324 (SEQ ID NO:324), Figure 326 (SEQ ID NO:326), Figure 328 (SEQ ID NO:328), Figure 330 (SEQ ID NO:330), Figure 332 (SEQ ID NO:332), Figure 334 (SEQ ID NO:334), Figure 336 (SEQ ID NO:336), Figure 338 (SEQ ID NO:338), Figure 340 (SEQ ID NO:340), Figure 342 (SEQ ID NO:342), Figure 344 (SEQ ID NO:344), Figure 346 (SEQ ID NO:346), Figure 348 (SEQ ID NO:348), Figure 350 (SEQ ID NO:350), Figure 352 (SEQ ID NO:352), Figure 354 (SEQ ID NO:354), Figure 356 (SEQ ID NO:356), Figure 358 (SEQ ID NO:358), Figure 360 (SEQ ID NO:360), Figure 362 (SEQ ID NO:362), Figure 364 (SEQ ID NO:364), Figure 366 (SEQ ID NO:366), Figure 368 (SEQ ID NO:368), Figure 370 (SEQ ID NO:370), Figure 372 (SEQ ID NO:372) or Figure 374 (SEQ ID NO:374), or agonist or antagonist thereof.

32. The method of Claim 31, wherein said agonist is an antibody to said polypeptide.
33. The method of Claim 31, wherein said antagonist is an antibody to said polypeptide.
34. The method of Claim 31, wherein the mammal is human.
35. The method of Claim 31, wherein the nucleic acid molecule is administered via *ex vivo* gene therapy.
36. A method for inhibiting endothelial cell growth in a mammal comprising administering to the mammal a PRO229, PRO 238, PRO247, PRO444, PRO720, PRO827, PRO1007, PRO1029, PRO1075, PRO1184, PRO1190, PRO1195, PRO1274, PRO1279, PRO1419, PRO1474, PRO1477, PRO1488, PRO1782, PRO1890, PRO4302, PRO4405, PRO5725, PRO5776, PRO6006, PRO7436, PRO9771, PRO10008, PRO21384 or PRO28631 polypeptide or agonist thereof, wherein endothelial cell growth in said mammal is inhibited.
37. A method for stimulating endothelial cell growth in a mammal comprising administering to the mammal a PRO21, PRO181, PRO205, PRO214, PRO221, PRO231, PRO238, PRO241, PRO247, PRO256, PRO258, PRO263, PRO265, PRO295, PRO321, PRO322, PRO337, PRO363, PRO365, PRO533, PRO697,

PRO725, PRO771, PRO788, PRO791, PRO819, PRO828, PRO836, PRO846, PRO865, PRO1005, PRO1006, PRO1025, PRO1054, PRO1071, PRO1079, PRO1080, PRO1114, PRO1131, PRO1155, PRO1160, PRO1186, PRO1192, PRO1244, PRO1272, PRO1273, PRO1279, PRO1283, PRO1286, PRO1306, PRO1309, PRO1325, PRO1329, PRO1347, PRO1356, PRO1376, PRO1382, PRO1411, PRO1412, PRO1508, PRO1550, PRO1556, PRO1760, PRO1787, PRO1801, PRO1868, PRO1887, PRO3438, PRO3444, PRO4324, PRO4333, PRO4341, PRO4342, PRO4353, PRO4354, PRO4356, PRO4371, PRO4408, PRO4422, PRO4425, PRO4499, PRO5723, PRO5737, PRO6029, PRO6071, PRO9821, PRO9873, PRO10008, PRO10096, PRO19670, PRO20040, PRO20044, PRO21055 or PRO21384 polypeptide, or agonist thereof, wherein endothelial cell growth in said mammal is stimulated.

38. A method for inducing cardiac hypertrophy in a mammal comprising administering to the mammal a PRO21 polypeptide or agonist thereof, wherein cardiac hypertrophy in said mammal is induced.

39. A method for stimulating angiogenesis induced by a PRO1376 or PRO1449 polypeptide in a mammal comprising administering a therapeutically effective amount of said polypeptide to the mammal, wherein said angiogenesis is stimulated.

40. A method for inducing endothelial cell apoptosis comprising administering to the endothelial cell a PRO4302 polypeptide or agonist thereof, wherein apoptosis in said endothelial cell is induced.

41. A method for stimulating smooth muscle cell growth comprising administering to the smooth muscle cell a PRO162, PRO182, PRO204, PRO221, PRO230, PRO256, PRO258, PRO533, PRO697, PRO725, PRO738, PRO826, PRO836, PRO840, PRO846, PRO865, PRO982, PRO1025, PRO1029, PRO1071, PRO1083, PRO1134, PRO1160, PRO1182, PRO1184, PRO1186, PRO1192, PRO1274, PRO1279, PRO1283, PRO1306, PRO1308, PRO1325, PRO1337, PRO1338, PRO1343, PRO1376, PRO1387, PRO1411, PRO1412, PRO1415, PRO1434, PRO1474, PRO1550, PRO1556, PRO1567, PRO1600, PRO1754, PRO1758, PRO1760, PRO1787, PRO1865, PRO1868, PRO1917, PRO1928, PRO3438, PRO3562, PRO4333, PRO4345, PRO4353, PRO4354, PRO4408, PRO4430, PRO4503, PRO6714, PRO9771, PRO9820, PRO9940, PRO10096, PRO21055, PRO21184 or PRO21366 polypeptide, or agonist thereof, wherein smooth muscle cell growth in said smooth muscle cell is stimulated.

42. A method for inhibiting smooth muscle cell growth comprising administering to the smooth muscle cell a PRO181, PRO195, PRO1080, PRO1265, PRO1309, PRO1488, PRO4302, PRO4405 or PRO5725 polypeptide, or agonist thereof, wherein smooth muscle cell growth in said smooth muscle cell is stimulated.

43. A method for inducing endothelial cell tube formation comprising administering to the endothelial cell a PRO178, PRO195, PRO228, PRO301, PRO302, PRO532, PRO724, PRO730, PRO734, PRO793, PRO871,

PRO938, PRO1012, PRO1120, PRO1139, PRO1198, PRO1287, PRO1361, PRO1864, PRO1873, PRO2010, PRO3579, PRO4313, PRO4527, PRO4538, PRO4553, PRO4995, PRO5730, PRO6008, PRO7223, PRO7248 or PRO7261 polypeptide, or agonist thereof, wherein tube formation in said endothelial cell is induced.

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**FIGURE 1**

GCCCACGCGTCCGATGGCGTTTCACGTTTCGCGGCCTTCTGCTACATGCTGGCGCTGCTGCT  
CACTGCCGCGCTCATCTTCTTCGCCATTTGGCACATTATAGCATTTGATGAGCTGAAGAC  
TGATTACAAGAATCCTATAGACCAGTGTAATACCCTGAATCCCCTTGTAAGTCCCAGAGTA  
CCTCATCCACGCTTTCTTCTGTGTCATGTTTCTTTGTGCAGCAGAGTGGCTTACACTGGG  
TCTCAATATGCCCCTCTTGGCATATCATATTTGGAGGTATATGAGTAGACCAGTGATGAG  
TGGCCCAGGACTCTATGACCCTACAACCATCATGAATGCAGATATTCTAGCATATTGTCA  
GAAGGAAGGATGGTGCAAATTAGCTTTTTATCTTCTAGCATTTTTTTTACTACCTATATGG  
CATGATCTATGTTTTGGTGAGCTCTTAGAACAACACACAGAAGAATTGGTCCAGTTAAGT  
GCATGCAAAAAGCCACCAAATGAAGGGATTCTATCCAGCAAGATCCTGTCCAAGAGTAGC  
CTGTGGAATCTGATCAGTTACTTTAAAAAATGACTCCTTATTTTTTAAATGTTTCCACAT  
TTTTGCTTGTGGAAAGACTGTTTTTCATATGTTTATACTCAGATAAAGATTTTAAATGGTAT  
TACGTATAAATTAATATAAAATGATTACCTCTGGTGTGACAGGTTTGAAGTTGCACTTC  
TTAAGGAACAGCCATAATCCTCTGAATGATGCATTAATTACTGACTGTCCTAGTACATTG  
GAAGCTTTTGTATTATAGGAAGTTGTAGGGCTCATTTTGGTTTCATTGAAACAGTATCTAA  
TTATAAATTAGCTGTAGATATCAGGTGCTTCTGATGAAGTGAAATGTATATCTGACTAG  
TGGGAAACTTCATGGGTTTCCTCATCTGTCATGTCGATGATTATATATGGATACATTTAC  
AAAAATAAAAAGCGGGAATTTTCCCTTCGCTTGAATATTATCCCTGTATATTGCATGAAT  
GAGAGATTTCCCATATTTCCATCAGAGTAATAAATATACTTGCTTTAATTCTTAAGCATA  
AGTAAACATGATATAAAAAATATATGCTGAATTACTTGTGAAGAATGCATTTAAAGCTATT  
TTAAATGTGTTTTTATTTGTAAGACATTACTTATTAAGAAATTGGTTATTATGCTTACTG  
TTCTAATCTGGTGGTAAAGGTATTCTTAAGAATTTGCAGGTACTACAGATTTTCAAAACT  
GAATGAGAGAAAATTGTATAACCATCCTGCTGTTTCCTTTAGTGCAATACAATAAAACTCT  
GAAATTAAGACTC

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## **FIGURE 2**

MAFTFAAFCYMLALLLTAALIFFAIWHIIAFDELKTDYKNPIDQCNTLNPLVLPEYLIHA  
FFCVMFLCAAEWLTGLNMPLLAYHIWRYMSRPVMSGPGLYDPTTIMNADILAYCQKEGW  
CKLAFYLLAFFYYLYGMIYVLVSS

**Important features:**

**Signal peptide:**

amino acids 1-20

**Type II transmembrane domain:**

amino acids 11-31

**Other transmembrane domain:**

amino acids 57-77 and 123-143

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**FIGURE 3**

GGCTCAGAGGCCCCACTGGACCCTCGGCTCTTCCTTGGACTTCTTGTGTGTTCTGTGAGC  
TTCGCTGGATTTCAGGGTCTTGGGCATCAGAGGTGAGAGGGTGGGAAGGTCCGCCCGCATG  
GGGAAGCCCTGGCTGCGTGCGCTACAGCTGCTGCTCCTGCTGGGCGCGTCGTGGGCGCGG  
GCGGGCGCCCCGCGCTGCACCTACACCTTCGTGCTGCCCCGCGAGAAGTTCACGGGCGCT  
GTGTGCTGGAGCGGCCCCGCATCCACGCGGGCGACGCCCCGAGGCCGCCAACGCCAGCGAG  
CTGGCGGCGCTGCGCATGCGCGTCGGCCGCCACGAGGAGCTGTTACGCGAGCTGCAGAGG  
CTGGCGGCGGCGGACGGCGCCGTGGCCGGCGAGGTGCGCGCGCTGCGCAAGGAGAGCCGC  
GGCCTGAGCGCGCGCCTGGGCCAGTTGCGCGCGCAGCTGCAGCACGAGGCGGGGCCCGGG  
GCGGGCCCCGGGGCGGATCTGGGGGCGGAGCCTGCCGCGGCGCTGGCGCTGCTCGGGGAG  
CGCGTGCTCAACGCGTCCGCCGAGGCTCAGCGCGCAGCCGCCCGGTTCCACCAGCTGGAC  
GTCAAGTTCGCGAGCTGGCGCAGCTCGTCACCCAGCAGAGCAGTCTCATCGCCCGCCTG  
GAGCGCCTGTGCCCCGGGAGGCGCGGGCGGGCAGCAGCAGGTCTGCCGCCACCCCCACTG  
GTGCTGTGGTTCCGGTCCGTCTTGTGGGTAGCACCAGTGACACCAGTAGGATGCTGGAC  
CCAGCCCCAGAGCCCCAGAGAGACCAGACCCAGAGACAGCAGGAGCCCATGGCTTCTCCC  
ATGCCTGCAGGTACCCCTGCGGTCCCCACCAAGCCTGTGGGCCCCGTGGCAGGATTGTGCA  
GAGGCCCGCCAGGCAGGCCATGAACAGAGTGGAGTGTATGAACTGCGAGTGGGCCGTGTCAC  
GTAGTGTGAGTATGGTGTGAGCAGCAACTGGAGGGTGGAGGCTGGACTGTGATCCAGCGG  
AGGCAAGATGGTTCAGTCAACTTCTTCACTACCTGGCAGCACTATAAGGCGGGCTTTGGG  
CGGCCAGACGGAGAATACTGGCTGGGCCCTGAACCCGTGTATCAGCTGACCAGCCGTGGG  
GACCATGAGCTGCTGGTTCTCCTGGAGGACTGGGGGGGCGGTGGAGCACGTGCCCACTAT  
GATGGCTTCTCCCTGGAACCCGAGAGCGACCACTACCGCCTGCGGCTTGGCCAGTACCAT  
GGTGATGCTGGAGACTCTCTTCTCCTGGCACAATGACAAGCCCTTCAGCACCGTGGATAGG  
GACCGAGACTCCTATTCTGGTAACTGTGCCCTGTACCAGCGGGGAGGCTGGTGGTACCAT  
GCCTGTGCCCACTCCAACCTCAACGGTGTGTGGCACCACGGCGGCCACTACCGAAGCCGC  
TACCAGGATGGTGTCTACTGGGCTGAGTTTCGTGGTGGGGCATATTCTCTCAGGAAGGCC  
GCCATGCTCATTGCGGCCCTGAAGCTGTGACTCTGTGTTTCTCTGTCCCCCTAGGCCCTAG  
AGGACATTGGTCAGCAGGAGCCCAAGTTGTTCTGGCCACACCTTCTTTGTGGCTCAGTGC  
CAATGTGTCCACAGAACTTCCCACTGTGGATCTGTGACCCTGGGCGCTGAAAATGGGAC  
CCAGGAATCCCCCGTCAATATCTTGGCCTCAGATGGCTCCCCAAGGTCATTATATCT  
CGGTTTGAGCTCATATCTTATAATAACACAAAGTAGCCAC

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**FIGURE 4**

MGKPWLRALQLLLLLLGASWARAGAPRCTYTFVLPPQKFTGAVCWSGPASTRATPEAANAS  
ELAALRMVRGRHEELLRELQRLAAADGAVAGEVRALRKESRGLSARLGQLRAQLQHEAGP  
GAGPGADLGAEPAAALALLGERVLNASAEQAARFHHQLDVKFRELAQLVTQSSLIAR  
LERLCPCGGAGGQQQVLPPPPLVPVVPVRLVGSTSDTSRMLDPAPEPORDQTQRQQEPMAS  
PMPAGHPAVPTKPVGPWQDCAEARQAGHEQSGVYELRVGRHVSVWCEQQLEGGGWTVIQ  
RRQDGSVNFFTTWQHYKAGFGRPDGEYWLGLEPVYQLTSRGDHELLVLLEDWGGRGARAH  
YDGFSLPEPESDHYRLRLGQYHGDAGDSLWHNDKPFSTVDRDRDSYSGNCALYQRGGWWY  
HACAHSNLNGVWHHGGHYRSRYQDGVYWAEFRGGAYSLRKAAMLIRPLKL

**Signal peptide:**

Amino acids 1-20

**N-glycosylation sites:**

Amino acids 58-62;145-149

**cAMP- and cGMP-dependent protein kinase phosphorylation site:**

Amino acids 97-101

**Tyrosine kinase phosphorylation site:**

Amino acids 441-448

**N-myristoylation sites:**

Amino acids

16-22;23-29;87-93;108-114;121-127;125-131;129-135;187-193;293-299;353-359;378-384;445-451;453-459

**Cell attachment sequence:**

Amino acids 340-343

**Fibrinogen beta and gamma chains C-terminal domain signature:**

Amino acids 418-431

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**FIGURE 5**

CCCACGCGTCCGGCGCCGCTGGCCTCGCGTCCATCTTTGCCGTTCTCTCGGACCTGTCACA  
AAGGAGTCGCGCCGCGCCGCGCCCGCCCCCTCCCTCCGGTGGGCCCCGGGAGGTAGAGAAAGT  
CAGTGCCACAGCCCGACCGCGCTGCTCTGAGCCCTGGGCACGCGGAACGGGAGGGAGTCT  
GAGGGTTGGGGACGTCTGTGAGGGAGGGGAACAGCCGCTCGAGCCTGGGGCGGGCGGACC  
GGACTGGGGCCGGGGTAGGCTCTGGAAAGGGCCCCGGGAGAGAGGTGGCGTTGGTCAGAAC  
CTGAGAAACAGCCGAGAGGTTTTCCACCGAGGCCCCGCGCTTGAGGGATCTGAAGAGGTTCT  
CTAGAAGAGGGTGTTCCTCTTTCCGGGGTCTCACCAGAAGAGGTTCTTGGGGGTGCGC  
CTTCTGAGGAGGCTGCGGCTAACAGGGCCCAGAACTGCCATTGGATGTCCAGAATCCCCT  
GTAGTTGATAATGTTGGGAATAAGCTCTGCAACTTTCTTTGGCATTCAAGTTGTTAAAAAC  
AAATAGGATGCAAATTCCTCAACTCCAGGTTATGAAAACAGTACTTGAAAACTGAAAAC  
TACCTAAATGATCGTCTTTGGTTGGGCCGTTCTTAGCGAGCAGAAGCCTTGGCCAGGG  
TCTGTTGTTGACTCTCGAAGAGCACATAGCCCACTTCCTAGGGACTGGAGGTGCCGCTAC  
TACCATGGGTAAATTCCTGTATCTGCCGAGATGACAGTGGAACAGATGACAGTGTTGACAC  
CCAACAGCAACAGGCCGAGAACAGTGCAAGTACCCACTGCTGACACAAGGAGCCAACCACG  
GGACCTGTTCGGCCACCAAGGAGGGGCCGAGGACCTCATGAGCCAAGGAGAAAGAAACA  
AAATGTGGATGGGCTAGTGTTGGACACACTGGCAGTAATACGGACTCTTGTAGATAAGTA  
AGTATCTGACTCACGGTCACCTCCAGTGGAATGAAAAGTGTTCTGCCCGGAACCATGACT  
TTAGGACTCCTTCAGTTCCCTTAGGACATACTCGCCAAGCCTTGTGCTCACAGGGCAAAG  
GAGAATATTTTAATGCTCCGCTGATGGCAGAGTAAATGATAAGATTTGATGTTTTTGCTT  
GCTGTCATCTACTTTGTCTGGAAATGTCTAAATGTTTCTGTAGCAGAAAACACGATAAAG  
CTATGATCTTTATTAGAG



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## FIGURE 6

MIVFGWAVFLASRSLGQGLLLTLEEHIAHFLGTGGAATTMGNSCICRDDSGTDDSVDTQQ  
QQAENSAVPTADTRSQPRDPVRPPRRGRGPHEPRRKKQNVDGLVLDTLAVIRTLVDKO

**Signal peptide:**  
amino acids 1-16

**Casein kinase II phosphorylation site:**  
amino acids 22-26, 50-54, 113-117

**N-myristoylation site:**  
amino acids 18-24, 32-38, 34-40, 35-41, 51-57

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**FIGURE 7**

CGGACGCGTG GGGGAAACCCCTTCCGAGAAAACAGCAACAAGCTGAGCTGCTGTGACAGAG  
GGGAACAAGATGGCGGCGCCGAAGGGGAGCCTCTGGGTGAGGACCCAACCTGGGGCTCCCG  
CCGCTGCTGCTGCTGACCATGGCCTTGGCCGGAGGTTCCGGGACCGCTTCGGCTGAAGCA  
TTTGACTCGGTCTTGGGTGATACGGCGTCTTGCCACCGGGCCTGTCAGTTGACCTACCCC  
TTGCACACCTACCCTAAGGAAGAGGAGTTGTACGCATGTCAGAGAGGTTGCAGGCTGTTT  
TCAATTTGTCAGTTTGTGGATGATGGAATTGACTTAAATCGAACTAAATTGGAATGTGAA  
TCTGCATGTACAGAAGCATATTCCCAATCTGATGAGCAATATGCTTGCCATCTTGGTTGC  
CAGAATCAGCTGCCATTGCTGAACTGAGACAAGAACAACCTTATGTCCCTGATGCCAAAA  
ATGCACCTACTCTTTCTCTAACTCTGGTGAGGTCATTCTGGAGTGACATGATGGACTCC  
GCACAGAGCTTCATAACCTCTTCATGGACTTTTTATCTTCAAGCCGATGACGGAAAAATA  
GTTATATTCCAGTCTAAGCCAGAAATCCAGTACGCACCACATTTGGAGCAGGAGCCTACA  
AATTTGAGAGAATCATCTCTAAGCAAAATGTCCTATCTGCAAATGAGAAATTCACAAGCG  
CACAGGAATTTTCTTGAAGATGGAGAAAGTGATGGCTTTTTAAGATGCCTCTCTCTTAAC  
TCTGGGTGGATTTTAACTACAACTCTTGTCCTCTCGGTGATGGTATTGCTTTGGATTTGT  
TGTGCAACTGTTGCTACAGCTGTGGAGCAGTATGTTCCCTCTGAGAAGCTGAGTATCTAT  
GGTGACTTGGAGTTTATGAATGAACAAAAGCTAAACAGATATCCAGCTTCTTCTCTTG  
GTTGTTAGATCTAAACTGAAGATCATGAAGAAGCAGGGCCTCTACCTACAAAAGTGAAT  
CTTGCTCATTCTGAAATTTAAGCATTTTTCTTTTAAAGACAAGTGTAATAGACATCTAA  
AATTCCACTCCTCATAGAGCTTTTAAATGGTTTCATTGGATATAGGCCTTAAGAAATCA  
CTATAAATGCAAATAAAGTTACTCAATCTGTG

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**FIGURE 8**

MAAPKGSLWVRTQLGLPPLLLLLTMALAGGSGTASAEAFDSVLGDTASCHRAQLTYPLHT  
YPKEEELYACQRCRLFSICQFVDDGIDLNRKLECESACTEAYSQSDEQYACHLGCQNO  
LPFAELRQEQLMSLMPKMHLFPLTLVRSFWSDMMDSAQSFITSSWTFYLQADDGKIVIF  
QSKPEIQYAPHLEQEPTNLRESSLSKMSYLOMRNSQAHRNFLEDGESDGFLRCLSLNSGW  
ILTTTLVLSVMVLLWICCATVATAVEQYVPSEKLSIYGDLEFMNEQKLNRYPASSLVVVR  
SKTEDHEEAGPLPTKVNLAHSEI

**Important features:**

**Signal peptide:**

amino acids 1-31

**Transmembrane domain:**

amino acids 241-260

**N-glycosylation site:**

amino acids 90-93

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**FIGURE 9**

TATTTACCATATCAGATTCACATTCAGTCCTCAGCAAAATGAAGGGCTCCATTTTCACTC  
TGTTTTTATTCTCTGTCCTATTTGCCATCTCAGAAGTGCGGAGCAAGGAGTCTGTGAGAC  
TCTGTGGGCTAGAATACATACGGACAGTCATCTATATCTGTGCTAGCTCCAGGTGGAGAA  
GGCATCTGGAGGGGATCCCTCAAGCTCAGCAAGCTGAGACAGGAACTCCTTCCAGCTCC  
CACATAAACGTGAGTTTTCTGAGGAAAATCCAGCGCAAAACCTTCCGAAGGTGGATGCCT  
CAGGGGAAGACCGTCTTTGGGGTGGACAGATGCCCCACTGAAGAGCTTTGGAAGTCAAAGA  
AGCATTCAGTGATGTCAAGACAAGATTTACAACTTTGTGTTGCACTGATGGCTGTTCCA  
TGA CTGATTTGAGTGCTCTTTGCTAAGACAAGAGCAAATACCCAATGGGTGGCAGAGCTT  
TATCACATGTTTAATTACAGTGTTTTACTGCCTGGTAGAACTAATATTGTGTTATTAA  
AATGATGGCTTTTGGGTAGGCAAACTTCTTTTCTAAAAGGTATAGCTGAGCGGTTGAAA  
CCACAGTGATCTCTATTTTCTCCCTTTGCCAAGGTTAATGAACTGTTCTTTTCAAAATTCT  
ACTAATGCTTTGAAATTTCAAATGCTGCGCAAAATTGCAATAAAAATGCTATAAA

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**FIGURE 10**

MKGSIFTLFLFSVLFAISEVRSKESVRLCGLEYIRTVIYICASSRWRRLHLEGIPOAQQAE  
TGNSFQLPHKREFSEENPAQNLPKVDASGEDRLWGGQMPTEELWKSCKHVSMSRQDLQTL  
CCTDGCSMTDLSALC

**Important features:**

**Signal sequence:**

amino acids 1-18

**cAMP- and cGMP-dependent protein kinase phosphorylation  
site:**

amino acids 107-111

**N-myristoylation sites:**

amino acids 3-9, 52-58, 96-102, 125-131

**Insulin family signature:**

amino acids 121-136

**Insulin family proteins:**

amino acids 28-46

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**FIGURE 11**

CCCACGCGTCCGGACAAACTGGAGGTGAAAGGAGCTGGTACTGTCCACTGTGCTGTGCGGT  
GCTGAACCTGAGACGCGAGCGGACCAGTTGCTCCAGCACCTGAAGGCAACGCCCTCTTGC  
ACCTCTGTGCCCTGTGGGACCCGCTTCACCAACAGGACCCATATCAACTTGACAAAGGA  
GTGTGGTATCGGACGTGGGAGAGAGTCCTCTGTTTGCCACCTGGGCGCTCATTGAGGCGT  
GACTTTGGAGATTTCTATAGTTTTAGACCAAACATTTTTTTTTTTCCCGCTAAGACGAT  
CTTTTGAGAGTTTTTTTTTTTTATTGTGATTTATATTTCCACAGCGTTTAGGAATCTTTCT  
GGGGGACTTTTGTGACTGTTAAAATAAGGTGAAAAGCAATAAGGATGTTTAAGTGCTGGT  
CAGTTGTCTTGTTCTCGGATTCATTTTTCTGGAGTCGGAAGGAAGGCCAACCAGGAAG  
GAGGATATGGCCTTAAATCCTATCAGCCTCTAATGAGATTGCGACATAAGCAGGAAAAA  
ATCAAGAAAGTTCAGAGTCAAAGGATTTATGATTCAGGATGGCCCTTTTGGATCTTGTG  
AAAATAAGTACTGTGGTTTGGGAAGACACTGTGTTACCAGCAGAGAGACAGGGCAAGCAG  
AATGTGCCTGTATGGACCTTTGCAAACGTCCTACAAACCTGTGTGTGGATCTGACGGAG  
AATTCTATGAAAACCACTGTGAAGTGCACAGAGCTGCTTGCCTGAAAAACAAAAGATTA  
CCATTGTTCACAATGAAGACTGCTTCTTTAAAGGAGATAAGTGCAAGACTACTGAATACA  
GCAAGATGAAAAATATGCTATTAGATTTACAAAATCAAAAATATATTATGCAAGAAAATG  
AAAATCCTAATGGCGACGACATATCTCGGAAGAAGCTATTGGTGGATCAAATGTTTAAAT  
ATTTTGATGCAGACAGTAATGGACTTGTAGATATTAATGAACTAACTCAGGTGATAAAC  
AGGAAGAAGCTGGCAAGGATCTCTTTGATTGTACTTTGTATGTTCTATTGAAATATGATG  
ATTTTAATGCTGACAAGCACCTGGCTCTTGAAGAATTTTATAGAGCATTCGAAGTGATCC  
AGTTGAGTCTGCCAGAAGATCAGAACTAAGCATCACTGCAGCAACTGTGGGACAAAGTG  
CTGTTCTGAGCTGTGCCATTCAAGGAACCCTGAGACCTCCCATTTATCTGGAAGGAACA  
ATATTATTCTAAATAATTTAGATTTGGAAGACATCAATGACTTTGGAGATGATGGGTCCT  
TGTATATTACTAAGGTTACCACAACTCACGTTGGCAATTACACCTGCTATGCAGATGGCT  
ATGAACAAGTCTATCAGACTCACATCTTCCAAGTGAATGTTTCCTCCAGTCATCC

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**FIGURE 12**

MFKCWSVVLVLGFIFLESEGRPTKEGGYGLKSYQPLMRLRHKQEKNOESSRVKGFMIQDG  
PFGSCENKYCGLGRHCVTSRETGQAEACMDLCKRHYKPVCSDGEFYENHCEVHRAACL  
KKQKITIVHNEDCFFKGDKCKTTEYSKMKNMLLDLQNKYIMQENENPNGDDISRKKLLV  
DQMFKYFDADSNGLVDINELTQVIKQEELGKDLFDCTLYVLLKYDDFNADKHLALEEFYR  
AFQVIQLSLPEDQKLSITAATVGQSAVLSCAIQGTLRPPIIWKRNNIILNNLDLEDINDF  
GDDGSLYITKVTTTHVGNYTCYADGYEQVYQTHIFQVNVPPVI

**Signal sequence:**

Amino acids 1-20

**N-glycosylation site:**

Amino acids 318-322

**Tyrosine kinase phosphorylation sites:**

Amino acids 21-29;211-220

**N-myristoylation sites:**

Amino acids 63-69;83-89;317-323

**Prokaryotic membrane lipoprotein lipid attachment site:**

Amino acids 260-271

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**FIGURE 13**

TGCCGGGCTGCGGGGCGCCTTGACTCTCCCTCCACCCTGCCTCCTCGGGCTCCACTCGTC  
TGCCCTTGACTCCCGTCTCCTCCTGTCTCCGGCTTCCCAGAGCTCCCTCCTTATGGCA  
GCAGCTTCCCGGTCTCCGGCGCAGCTTCTCAGCGGACGACCCTCTCGCTCCGGGGCTGA  
GCCAGTCCCTGGATGTTGCTGAAACTCTCGAGATCATGCGCGGGTTTGGCTGCTGCTTC  
CCCGCCGGGTGCCACTGCCACCGCCGCCCTCTGCTGCCGCCGTCCGCGGGATGCTCAG  
TAGCCCGCTGCCCGGCCCCCGCGATCCTGTGTTCTCGGAAGCCGTTTGCTGCTGCAGAG  
TTGCACGAACTAGTCATGGTGCTGTGGGAGTCCCCGCGCAGTGCAGCAGCTGGACACTT  
TGCGAGGGCTTTTGCTGGCTGCTGCTGCTGCCCGTCATGCTACTCATCGTAGCCCGCCCG  
GTGAAGCTCGCTGCTTTCCCTACCTCCTTAAGTGAAGTGCCTAACGCCCCACCGGCTGGAAT  
TGCTCTGGTTATGATGACAGAGAAAATGATCTCTTCCCTCTGTGACACCAACACCTGTAAA  
TTTGATGGGGAATGTTTAAGAAATTGGAGACACTGTGACTTGCGTCTGTCAAGTCAAGTGC  
AACATGACTATGTGCTGTGTGTGGCTCCAATGGGGAGAGCTACCAGAATGAGTGTTAC  
CTGCGACAGGCTGCATGCAAACAGCAGAGTGAGATACTTGTGGTGTGAGAAGGATCATGT  
GCCACAGATGCAGGATCAGGATCTGGAGATGGAGTCCATGAAGGCTCTGGAGAACTAGT  
CAAAAGGAGACATCCACCTGTGATATTTGCCAGTTTGGTGCAGAATGTGACGAAGATGCC  
GAGGATGTCTGGTGTGTGTGTAATATTGACTGTTCTCAAACCAACTTCAATCCCCTCTGC  
GCTTCTGATGGGAAATCTTATGATAATGCATGCCAAATCAAAGAAGCATCGTGTGAGAAA  
CAGGAGAAAATTGAAGTCATGTCTTTGGGTGCGATGTCAAGATAACACAACACTACAACACT  
AAGTCTGAAGATGGGCATTATGCAAGAACAGATTATGCAGAGAATGCTAACAAATTAGAA  
GAAAGTGCCAGAGAACACCACATACCTTGTCCGGAACATTACAATGGCTTCTGCATGCAT  
GGGAAGTGTGAGCATTCTATCAATATGCAGGAGCCATCTTGCAGGTGTGATGCTGGTTAT  
ACTGGACAACACTGTGAAAAAAGGACTACAGTGTTCTATACGTTGTTCCCGGTCCTGTA  
CGATTTCAAGTATGTCTTAATCGCAGCTGTGATTGGAACAATTCAGATTGCTGTCATCTGT  
GTGGTGGTCTCTGCATCACAAGGAAATGCCCCAGAAAGCAACAGAATTCACAGACAGAAG  
CAAAATACAGGGCACTACAGTTCAGACAATAACAAGAGCGTCCACGAGGTTAATCTAA  
AGGGAGCATGTTTCACAGTGGCTGGACTACCGAGAGCTTGGACTACACAATACAGTATTA  
TAGACAAAAGAAATAAGACAAGAGATCTACACATGTTGCCTTGCATTTGTGGTAATCTACA  
CCAATGAAAACATGTACTACAGCTATATTTGATTATGTATGGATATATTTGAAATAGTAT  
ACATTGTCTTGATGTTTTTTCTGTAATGTAAATAAACTATTTATATCACACAATATAGTT  
TTTTCTTTCCCATGTATTTGTTATATATAATAAATACTCAGTGATGAG



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**FIGURE 14**

MVLWESPRQCSSWTLCEGFCWLLLLLPVMLLIVARPVKLA AFPTSLSDCQTPTGWNC SGY  
DDRENDLFLCDTNTCKFDGECLRIGDTVTCVCQFKCNNDYVPVCGSNGESYQNECYLRQ  
AACKQQSEILVVSEGSCATDAGSGSGDGVHEGSGETSQKETSTCDICQFGAECDEDAED  
VWCVCNIDCSQTNFNPLCASDGKSYDNACQIKEASCQKQEKIEVMSLGRCQDNTTTT TK  
SEDGHYARTDYAENANKLEESAREHHIPCPEHYNGFCMHGKCEHSINMQEPSCRC DAGY  
TGQHCEKKDYSVLYVVP GPVRFQYVLIAAVIGTIQIAVICVVVLCITRKCPRSNRIHRQ  
KQNTGHYSSDNTTRASTRLI

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**FIGURE 15**

GGAGCTCAGCCCAGTGGGCAGTCTGAAGATGGCCAATTACACGCTGGCACCAGAGGATGA  
ATATGATGTCCTCATAGAAGGTGAACTGGAGAGCGATGAGGCAGAGCAATGTGACAAGTA  
TGACGCCCAGGCACTCTCAGCCCAGCTGGTGCCATCACTCTGCTCTGCTGTGTTTGTGAT  
CGGTGTCCTGGACAATCTCCTGGTTGTGCTTATCCTGGTAAAATATAAAGGACTCAAACG  
CGTGGAATAATATCTATCTTCTAAACTTGGCAGTTTCTAACTTGTGTTTCTTGCTTACCCT  
GCCCTTCTGGGCTCATGCTGGGGGCGATCCCATGTGTAAAATTCTCATTTGGACTGTACTT  
CGTGGGCCTGTACAGTGAGACATTTTCAATTGCCTTCTGACTGTGCAAAGGTACCTAGT  
GTTTTTGCACAAGGGCAACTTTTTCTCAGCCAGGAGGAGGGTGGCCTGTGGCATCATTAC  
AAGTGTCCTGGCATGGGTAAACAGCCATTCTGGCCACTTTGCCTGAATACGTGGTTTATAA  
ACCTCAGATGGAAGACCAGAAATACAAGTGTGCATTTAGCAGAACTCCCTTCCTGCCAGC  
TGATGAGACATTCTGGAAGCATTCTTGACTTTAAAAATGAACATTTTCGGTTCTTGTCCT  
CCCCCTATTTATTTTACATTTCTCTATGTGCAAATGAGAAAAACACTAAGGTTCAGGGA  
GCAGAGGTATAGCCTTTTCAAGCTTGTTTTTGCCATAATGGTAGTCTTCCTTCTGATGTG  
GGCGCCCTACAATATTGCATTTTCTGTCCACTTTCAAAGAACACTTCTCCCTGAGTGA  
CTGCAAGAGCAGCTACAATCTGGACAAAAGTGTTCACATCACTAACTCATCGCCACCAC  
CCACTGCTGCATCAACCCTCTCCTGTATGCGTTTCTTGATGGGACATTTAGCAAATACCT  
CTGCCGCTGTTTCCATCTGCGTAGTAACACCCCACTTCAACCCAGGGGGCAGTCTGCACA  
AGGCACATCGAGGGAAGAACCTGACCATTCACCCGAAGTGTA~~AA~~ACTAGCATCCACCAAAT  
GCAAGAAGAATAAACATGGATTTTCATCTTTCTGCATTATTTTCATGTAAATTTTCTACAC  
ATTTGTATACAAAATCGGATACAGGAAGAAAAGGGAGAGGTGAGCTAACATTTGCTAAGC  
ACTGAATTTGTCTCAGGCACCGTGCAAGGCTCTTTACAAACGTGAGCTCCTTCGCCCTCCT  
ACCACTTGTCCATAGTGTGGATAGGACTAGTCTCATTTCTCTGAGAAGAAAATAAGGCG  
CGGAAATTTGTCTAAGATCACATAACTAGGAAGTGGCAGAACTGATTCTCCAGCCCTGGT  
AGCATTTGCTCAGAGCCTACGCTTGGTCCAGAACATCAAACCTCAAACCCTGGGGACAAA  
CGACATGAAATAAATGTATTTTAAACATCTAAAA

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**FIGURE 16**

MANYTLAPEDEYDVLIIEGELESDEAEQCDKYDAQALSAQLVPSLCSAVFVIGVLDNLLVV  
LILVKYKGLKRVENIYLLNLAVSNLCFLLTLFPAHAGGDPCKILIGLYFVGLYSETFF  
NCLLTVQRYLVFLHKGNNFSARRRVPCGIITSVLAWVTAILATLPEYVVYKQMEDQKYK  
CAFSRTPFLPADETFWKHFLTLKMNIISVLVPLFIPTFLYVQMRKTLRFREORYSLFKLV  
FAIMVVFLMWAPYNIAFFLSTFKEHFSLSDCSSYNLDKSVHITKLIATTHCCINPLLY  
AFLDGTFSKYLRCRCFHLRSNTPLQPRGQSAQGTSREEPDHSTEV

**Signal sequence:**

None

**Transmembrane domain:**

41-61, 76-96, 109-129, 147-167, 199-219, 237-257, 285-305

**7. transmembrane receptor (rhodopsin family):**

55-300

**N-glycosylation site:**

3-6, 205-208

**Tyrosine kinase phosphorylation site:**

70-76, 171-179, 228-234

**N-myristoylation site:**

52-57, 136-141, 148-153

**G-protein coupled receptors:**

55-85, 96-136, 209-220, 235-254, 292-308

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**FIGURE 17**

CGGACGCGTGGGCGGACGCGTGGGCGGCCACGGCGCCCGCGGGCTGGGGCGGTGCGTTCTC  
TTCCTTCTCCGTGGCCTACGAGGGTCCCCAGCCTGGGTAAAGATGGCCCCATGGCCCCCG  
AAGGGCCTAGTCCCAGCTGTGCTCTGGGGCCTCAGCCTCTTCTCAACCTCCCAGGACCT  
ATCTGGCTCCAGCCCTCTCCACCTCCCCAGTCTTCTCCCCCGCCTCAGCCCCATCCGTGT  
CATACCTGCCGGGGACTGGTTGACAGCTTTAACAAGGGCCTGGAGAGAACCATCCGGGAC  
AACTTTGGAGGTGGAAACACTGCCTGGGAGGAAGAGAAATTTGTCCAAATACAAAGACAGT  
GAGACCCGCTGGTAGAGGTGCTGGAGGGTGTGTGCAGCAAGTCAGACTTCGAGTGCCAC  
CGCCTGCTGGAGCTGAGTGAGGAGCTGGTGGAGAGCTGGTGGTTTCACAAGCAGCAGGAG  
GCCCCGACCTCTTCCAGTGGCTGTGCTCAGATTCCCTGAAGCTCTGCTGCCCCGCAGGC  
ACCTTCGGGGCCCTCCTGCCTTCCCTGTCTGGGGGAACAGAGAGGCCCTGCGGTGGCTAC  
GGGCAGTGTGAAGGAGAAGGGACACGAGGGGGCAGCGGGCACTGTGACTGCCAAGCCGGC  
TACGGGGGTGAGGCCTGTGGCCAGTGTGGCCTTGGCTACTTTGAGGCAGAACGCAACGCC  
AGCCATCTGGTATGTTTCGGCTTGTTTGGCCCCCTGTGCCCGATGCTCAGGACCTGAGGAA  
TCAAACGTGTTTGCAATGCAAGAAGGGCTGGGCCCTGCATCACCTCAAGTGTGTAGACATT  
GATGAGTGTGGCACAGAGGGAGCCAACTGTGGAGCTGACCAATTCTGCGTGAACACTGAG  
GGCTCCTATGAGTGCCGAGACTGTGCCAAGGCCTGCCTAGGCTGCATGGGGGCAGGGCCA  
GGTCGCTGTAAGAAGTGTAGCCCTGGCTATCAGCAGGTGGGCTCCAAGTGTCTCGATGTG  
GATGAGTGTGAGACAGAGGTGTGTCCGGGAGAGAAACAAGCAGTGTGAAAACACCGAGGGC  
GGTTATCGCTGCATCTGTGCCGAGGGCTACAAGCAGATGGAAGGCATCTGTGTGAAGGAG  
CAGATCCCAGAGTCAGCAGGCTTCTTCTCAGAGATGACAGAAGACGAGTTGGTGGTGCTG  
CAGCAGATGTTCTTTGGCATCATCATCTGTGCACTGGCCACGCTGGCTGCTAAGGGCGAC  
TTGGTGTTCACCGCCATCTTCATTGGGGCTGTGGCGGCCATGACTGGCTACTGGTTGTCA  
GAGCGCAGTGACCGTGTGCTGGAGGGCTTCATCAAGGGCAGATAATCGCGGCCACCACCT  
GTAGGACCTCCTCCCACCCACGCTGCCCCCAGAGCTTGGGCTGCCCTCCTGCTGGACACT  
CAGGACAGCTTGGTTTATTTTTGAGAGTGGGGTAAGCACCCCTACCTGCCTTACAGAGCA  
GCCCAGGTACCCAGGCCCGGGCAGACAAGGCCCTGGGGTAAAAAGTAGCCCTGAAGGTG  
GATACCATGAGCTCTTCACCTGGCGGGGACTGGCAGGCTTCACAAATGTGTGAATTTCAA  
AGTTTTTCCTTAATGGTGGCTGCTAGAGCTTTGGCCCCCTGCTTAGGATTAGGTGGTCCTC  
ACAGGGGTGGGGCCATCACAGCTCCCTCCTGCCAGCTGCATGCTGCCAGTTCTCTGTTCTG  
TGTTACACCATCCCCACACCCATTGCCACTTATTTATTTCATCTCAGGAAATAAAGAAA  
GGTCTTGGAAGTTAAAAA

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**FIGURE 18**

MAPWPPKGLVPAVLWGLSLFLNLPGPPIWLQSPPPQSSPPPQPHPCHTCRGLVDSFNKGL  
ERTIRDNFGGGNTAWEEENLSKYKDSETRLVEVLEGVCSKSDFECHRLLELSEELVESWW  
FHKQQEAPDLFQWLCSDSLKLCCPAGTFGPSCLPCPGGTERPCGGYGQCEGEGTRGSGH  
CDCQAGYGGEACGQCGLGYFEARNASHLVCSACFGPCARCSGPEESNCLQCKKGWALHH  
LKCVDIDECGTEGANCGADQFCVNTEGSYECRDCAKACLGCMGAGPGRCKKCSPGYQQVG  
SKCLDVDECETEVCPGENKQCENTEGGYRCICAEGYQMEGICVKEQIPESAGFFSEMTE  
DELVVLQQMFFGIIICALATLAAKGLVFTAIFIGAVAAMTGYWLSERSDRVLEGFIKGR

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**FIGURE 19**

GCCCCGGGACTGGCGCAAGGTGCCCAAGCAAGGAAAGAAATAATGAAGAGACACATGTGT  
AGCTGCAGCCTTTTGAACACGCAAGAAGGAAATCAATAGTGTGGACAGGGCTGGAACCT  
TTACCACGCTTGTTGGAGTAGATGAGGAATGGGCTCGTGATTATGCTGACATTCCAGCAT  
GAATCTGGTAGACCTGTGGTTAACCCGTTCCCTCTCCATGTGTCTCCTCCTACAAAGTTT  
TGTTCTTATGATACTGTGCTTTTCATTCTGCCAGTATGTGTCCCAAGGGCTGTCTTTGTTC  
TTCCTCTGGGGGTTTAAATGTACCTGTAGCAATGCAAATCTCAAGGAAATACCTAGAGA  
TCTTCCTCCTGAAACAGTCTTACTGTATCTGGACTCCAATCAGATCACATCTATTCCCAA  
TGAAATTTTAAAGGACCTCCATCAACTGAGAGTTCTCAACCTGTCCAAAAATGGCATTGA  
GTTTATCGATGAGCATGCCTTCAAAGGAGTAGCTGAAACCTTGCAGACTCTGGACTTGTC  
CGACAATCGGATTCAAAGTGTGCACAAAAATGCCTTCAATAACCTGAAGGCCAGGGCCAG  
AATTGCCAACCAACCCCTGGCACTGCGACTGTACTCTACAGCAAGTTCTGAGGAGCATGGC  
GTCCAATCATGAGACAGCCCACAACGTGATCTGTAAAACGTCCGTGTTGGATGAACATGC  
TGGCAGACCATTCCTCAATGCTGCCAACGACGCTGACCTTTGTAACCTCCCTAAAAAAAC  
TACCGATTATGCCATGCTGGTCACCATGTTTGGCTGGTTCACTATGGTGATCTCATATGT  
GGTATATTATGTGAGGCAAAATCAGGAGGATGCCCGGAGACACCTCGAATACTTGAAATC  
CCTGCCAAGCAGGCAGAAGAAAGCAGATGAACCTGATGATATTAGCACTGTGGTATAGTG  
TCCAAACTGACTGTGATTGAGAAAGAAAGAAAGTAGTTTGCGATTGCAGTAGAAATAAGT  
GGTTTACTTCTCCCATCCATTGTAAACATTTGAACTTTGTATTTTCAGTTTTTTTTTGAAT  
TATGCCACTGCTGAACTTTTAACAAACACTACAACATAAATAATTTGAGTTTAGGTGATC  
CACCCCTTAATTGTACCCCGATGGTATATTTCTGAGTAAGCTACTATCTGAACATTAGT  
TAGATCCATCTCACTATTTAATAATGAAATTTATTTTTTTAATTTAAAAGCAAATAAAAG  
CTTAACTTTGAACCATGGGAAAAAAAAAAAAAAAAAAAAAAAAAACA

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**FIGURE 20**

MNLVDLWLTRSLSMCLLLQSFVLMILCFHSASMCPKGCLCSSSGGLNVTCSNANLKEIPR  
DLPPETVLLYLDNQITSIPNEIFKDLHQLRVNLNSKNGIEFIDEHAFKGVAETLQTLDL  
SDNRIQSVHKNAFNNLKARARIANNPWHCDCTLQQVLRSMASNHETAHNVICKTSVLDEH  
AGRPFLNAANDADLCNLPKKTDDYAMLVTMFGWFTMVISYVVYYVRQNQEDARRHLEYLK  
SLPSRQKKADEPDDISTVV

**Signal sequence:**  
amino acids 1-33

**Transmembrane domain:**  
amino acids 205-220

**N-glycosylation site:**  
amino acids 47-51, 94-98

**cAMP- and cGMP-dependent protein kinase phosphorylation site:**  
amino acids 199-203

**Casein kinase II phosphorylation site:**  
amino acids 162-166, 175-179

**N-myristoylation site:**  
amino acids 37-43, 45-51, 110-116

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**FIGURE 21**

CGCCACCACTGCGGCCACCGCCAATGAAACGCCTCCCGCTCCTAGTGGTTTTTTTCCACTT  
TGTTGAATTGTTTCTTATACTCAAAATTGCACCAAGACACCTTGTCTCCCAAATGCAAAAT  
GTGAAATACGCAATGGAATTGAAGCCTGCTATTGCAACATGGGATTTTTCAGGAAATGGTG  
TCACAATTTGTGAAGATGATAATGAATGTGGAAATTTAACTCAGTCCTGTGGCGAAAATG  
CTAATTGCACTAACACAGAAGGAAGTTATTATTGTATGTGTGTACCTGGCTTCAGATCCA  
GCAGTAACCAAGACAGGTTTATCACTAATGATGGAACCGTCTGTATAGAAAATGTGAATG  
CAAAC TGCCATTTAGATAATGTCTGTATAGCTGCAAATATTAATAAACTTTAACAAAAA  
TCAGATCCATAAAAGAACCTGTGGCTTTGCTACAAGAAGTCTATAGAAATTCGTGTACAG  
ATCTTTCACCAACAGATATAATTACATATATAGAAATATTAGCTGAATCATCTTCATTAC  
TAGGTTACAAGAACAACACTATCTCAGCCAAGGACACCCTTTCTAACTCAACTCTTACTG  
AATTTGTAAAAACCGTGAATAATTTTGTTCAAAGGGATACATTTGTAGTTTGGGACAAGT  
TATCTGTGAATCATAGGAGAACACATCTTACAAAACCTCATGCACACTGTTGAACAAGCTA  
CTTTAAGGATATCCCAGAGCTTCCAAAAGACCACAGAGTTTGATACAAATTCAACGGATA  
TAGCTCTCAAAGTTTTCTTTTTTGATTATATAACATGAAACATATTTCATCCTCATATGA  
ATATGGATGGAGACTACATAAATATATTTCCAAAGAGAAAAGCTGCATATGATTCAAATG  
GCAATGTTGCAGTTGCATTTTTATATTATAAGAGTATTGGTCCTTTGCTTTCATCATCTG  
ACAAC TTTCTATTGAAACCTCAAAATTATGATAATTCTGAAGAGGAGGAAAAGAGTCATAT  
CTTCAGTAATTTAGTCTCAATGAGCTCAAACCCACCCACATTATATGAAC TTGAAAAAA  
TAACATTTACATTAAAGTCATCGAAAGGTCACAGATAGGTATAGGAGTCTATGTGCATTTT  
GGAATTACTCACCTGATACCATGAATGGCAGCTGGTCTTCAGAGGGCTGTGAGCTGACAT  
ACTCAAATGAGACCCACACCTCATGCCGCTGTAATCACCTGACACATTTTGCATTTTGA  
TGTCTCTGGTCCTTCCATTGGTATTAAAGATTATAATATTCTTACAAGGATCACTCAAC  
TAGGAATAATTATTTCACTGATTTGTCTTGCCATATGCATTTTTACCTTCTGGTTCTTCA  
GTGAAATTCAAAGCACCCAGGACAACAATTCACAAAAATCTTTGCTGTAGCCTATTTCTTG  
CTGAAC TTGTTTTCTTGTGGGATCAATACAAATACTAATAAGCTCTTCTGTTCAATCA  
TTGCCGGA CTGTACACTACTTCTTTTTAGCTGCTTTTGCATGGATGTGCATTGAAGGCA  
TACATCTCTATCTCATTGTTGTGGGTGTCTATACAACAAGGGATTTTTGCACAAGAATT  
TTTATATCTTTGGCTATCTAAGCCAGCCGTGGTAGTTGGATTTTCGGCAGCACTAGGAT  
ACAGATATTATGGCACAACCAAAGTATGTTGGCTTAGCACCGAAAACAAC TTTATTTGGA  
GTTTTATAGGACCAGCATGCCTAATCATTCTTGTTAATCTCTTGGCTTTTGGAGTCATCA  
TATACAAAGTTTTTCGTCACACTGCAGGGTTGAAACCAGAAGTTAGTTGCTTTGAGAAC  
TAAGGTCTTGTGCAAGAGGAGCCCTCGCTCTTCTGTTCTCTCGGCACCACCTGGATCT  
TTGGGGTTCTCCATGTTGTGCACGCATCAGTGGTTACAGCTTACCTCTTCACAGTCAGCA  
ATGCTTTCCAGGGGATGTTCAATTTTTTTATTCCCTGTGTGTTTTATCTAGAAAGATTCAAG  
AAGAATATTACAGATTGTTCAAAAATGTCCCCTGTTGTTTTGGATGTTTAAGGTAAACAT  
AGAGAATGGTGGATAATTACAAC TGCAAAAAATAAAAAATCCAAGCTGTGGATGACCAA  
TGTATAAAAATGACTCATCAAATTATCCAATTATTAAC TACTAGACAAAAAGTATTTTAA  
ATCAGTTTTTCTGTTTATGCTATAGGAACTGTAGATAATAAGGTAAAATTATGTATCATA  
TAGATATACTATGTTTTCTATGTGAAATAGTTCTGTCAAAAATAGTATTGCAGATATTT  
GGAAAGTAATTGGTTTTCTCAGGAGTGATATCACTGCACCCAAGGAAAGATTTTCTTTCTA  
ACACGAGAAGTATATGAATGTCCTGAAGGAAACCACTGGCTTGATATTTCTGTGACTCGT  
GTTGCCTTTGAAACTAGTCCCCTACCACCTCGGTAATGAGCTCCATTACAGAAAGTGGA  
CATAAGAGAATGAAGGGGCAGAATATCAAACAGTGAAAAGGGAATGATAAGATGTATTTT  
GAATGAACTGTTTTTTCTGTAGACTAGCTGAGAAATTGTTGACATAAAATAAAGAATTGA  
AGAAACACATTTTACCATTTTGTGAATTGTTCTGAACTTAAATGTCCACTAAAACAAC TT  
AGACTTCTGTTTGTCTAAATCTGTTTCTTTTTCTAATATTCTAAAAA AAAAAAAAAAAGGTTT  
ACCTCCACAAATTGAAAAA AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA



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**FIGURE 22**

MKRLPLLVVFSTLLNCSYTONCTKTPCLPNAKCEIRNGIEACYCNMGFSGNGVTICEDDN  
ECGNLTQSCGENANCTNTEGSYYCMVPGFRSSSNQDRFITNDGTVCIENVNANCHLDNV  
CIAANINKTLTKIRSIKEPVALLOEVYRNSVTDLSPTDIITYIEILAESSLLGYKNNTI  
SAKDTLSNSTLTEFVKTVNNFVQRDTFVVWDKLSVNHRRTHLTKLMHTVEQATLRISQSF  
QKTTEFDTNSTDIALKVFFFDSDYNMKHIHPHMNMDGDYINIFPKRKAAYDSNGNVAVAF  
YYKSIGPLLSSSDNFLLPQNYDNSEEEERVISVISVSMSSNPPTLYELEKITFTLSHR  
KVTDYRSLCAFWNYSPTMNGSWSSEGCETYSNETHTSCRCNHLTHFAILMSSGPSIG  
IKDYNILTRITQLGIIISLICLAICIFTFWFFSEIQSTRTTIHKNLCCSLFLAELVFLVG  
INTNTNKLFCSEIIAGLLHYFFLAFAWMCIEGIHLYLIVVGVIYNKGFLHKNFYIFGYLS  
PAVVVGFSALGYRYYGTTKVCWLSTENNFIWSFIGPACLIILVNLLAFGVIIYKVFRHT  
AGLKPEVSCFENIRSCARGALALLFLLGTTWIFGVLHVHVASVVTAYLFTVSNAFQGMFI  
FLFLCVLSRKIQEYYRLFKNPCCFGCLR

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**FIGURE 23**

CTCCTCTTAACATACTTGCAGCTAAACTAAATATTGCTGCTTGGGGACCTCCTTCTAGC  
CTTAAATTTT CAGCTCATCACCTTCACCTGCCTTGGTCATGGCTCTGCTATTCTCCTTGAT  
CCTTGCCATTTGCACCAGACCTGGATTCCCTAGCGTCTCCATCTGGAGTGCGGCTGGTGGG  
GGGCCTCCACCGCTGTGAAGGGCGGGTGGAGGTGGAACAGAAAGGCCAGTGGGGCACCGT  
GTGTGATGACGGCTGGGACATTAAGGACGTGGCTGTGTTGTGCCGGGAGCTGGGCTGTGG  
AGCTGCCAGCGGAACCCCTAGTGGTATTTTGTATGAGCCACCAGCAGAAAAAGAGCAAAA  
GGTCCTCATCCAATCAGTCAGTTGCACAGGAACAGAAGATACATTGGCTCAGTGTGAGCA  
AGAAGAAGTTTATGATTGTTTACATGATGAAGATGCTGGGGCATCGTGTGAGAACCCAGA  
GAGCTCTTTCTCCCCAGTCCCAGAGGGTGTGAGGCTGGCTGACGGCCCTGGGCATTGCAA  
GGGACGCGTGGAAGTGAAGCACCAAGACAGTGGTATACCGTGTGCCAGACAGGCTGGAG  
CCTCCGGGCCGCAAAGGTGGTGTGCCGGCAGCTGGGATGTGGGAGGGCTGTACTGACTCA  
AAAACGCTGCAACAAGCATGCCTATGGCCGAAAACCCATCTGGCTGAGCCAGATGTCATG  
CTCAGGACGAGAAGCAACCCTTCAGGATTGCCCTTCTGGGCCTTGGGGGAAGAACACCTG  
CAACCATGATGAAGACACGTGGGTGCAATGTGAAGATCCCTTTGACTTGAGACTAGTAGG  
AGGAGACAACCTCTGCTCTGGGCGACTGGAGGTGCTGCACAAGGGCGTATGGGGCTCTGT  
CTGTGATGACAACTGGGGAGAAAAGGAGGACCAGGTGGTATGCAAGCAACTGGGCTGTGG  
GAAGTCCCTCTCTCCCTCCTTCAGAGACCGGAAATGCTATGGCCCTGGGGTTGGCCGCAT  
CTGGCTGGATAATGTTGTTGCTCAGGGGAGGAGCAGTCCCTGGAGCAGTGCCAGCACAG  
ATTTTGGGGGTTTCACGACTGCACCCACCAGGAAGATGTGGCTGTCATCTGCTCAGTGTA  
GGTGGGCATCATCTAATCTGTTGAGTGCCTGAATAGAAGAAAAACACAGAAGAAGGGAGC  
ATTTACTGTCTACATGACTGCATGGGATGAACACTGATCTTCTTCTGCCCTTGGACTGGG  
ACTTATACTTGGTGCCCCCTGATTCTCAGGCCTTCAGAGTTGGATCAGAACTTACAACATC  
AGGTCTAGTTCTCAGGCCATCAGACATAGTTTGGAACCTACATCACCACCTTTCTATGTC  
TCCACATTGCACACAGCAGATTCCCAGCCTCCATAATTGTGTGTATCAACTACTTAAATA  
CATTCTCACACACACACACACACACACACACACACACATACACCATTTGTCC  
TGTTTCTCTGAAGAACTCTGACAAAATACAGATTTTGGTACTGAAAGAGATTCTAGAGGA  
ACGGAATTTTAAAGGATAAAATTTTCTGAATTGGTTATGGGGTTTCTGAAATTGGCTCTATA  
ATCTAATTAGATATAAAATTTCTGGTAACTTTATTTACAATAATAAAGATAGCACTATGTG  
TTCAAA

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**FIGURE 24**

MALLFSLILAICTRPGFLASPSGVRLVGGLHRCEGRVEVEQKGQWGTVCDDGWDIKDVAV  
LCRELGCCGAASGTPSGILYEPPAEKEQKVLIQSVSCTGTEDTLAQCEQEVEYDCSHDEDA  
GASCENPESSFSPVPEGVRLADGPGHCKGRVEVKHQNQWYTVCTGWSLRAAKVVCRLG  
CGRAVLTQKRCNKHAYGRKPIWLSQMSCSGREATLQDCPSGPWGKNTCNHDEDTWVECED  
PFDLRLVGDNLCSEGRLEVLHKGWGSVCDDNWGEKEDQVVCCKQLGCGKSLSPSFRDRKC  
YGPVGRIWLDNVRCSGEEQSLEQCQHRFWGFHDCTHQEDVAVICSV

**Signal sequence:**

amino acids 1-15

**Casein kinase II phosphorylation site:**amino acids 47-51, 97-101, 115-119, 209-213, 214-218, 234-238,  
267-271, 294-298, 316-320, 336-340**N-myristoylation site:**amino acids 29-35, 43-49, 66-72, 68-74, 72-78, 98-104, 137-143,  
180-186, 263-269, 286-292**Amidation site:**

amino acids 196-200

**Speract receptor repeated domain signature:**

amino acids 29-67, 249-287

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**FIGURE 25**

CGGACGCGTGGGCGTCCGGCGGTTCGACAGCCAGGAGGCGGAGGCGCGGGCCAGCCTG  
GGCCCCAGCCACACCTTCACCAGGGCCCAGGAGCCACCAATGTGGCGATGTCCACTGGGG  
CTACTGCTGTTGCTGCCGCTGGCTGGCCACTTGGCTCTGGGTGCCCAGCAGGGTCGTGGG  
CGCCGGGAGCTAGCACCGGGTCTGCACCTGCCGGGCATCCGGGACGCGGGAGGCCGGTAC  
TGCCAGGAGCAGGACCTGTGCTGCCGCGGCCGTGCCGACGACTGTGCCCTGCCCTACCTG  
GGCGCCATCTGTTACTGTGACCTCTTCTGCAACCGCACGGTCTCCGACTGCTGCCCTGAC  
TTCTGGGACTTCTGCCTCGGCGTGCCACCCCTTTTCCCCCGATCCAAGGATGTATGCAT  
GGAGGTCGTATCTATCCAGTCTTGGGAACGTACTGGGACAACTGTAACCGTTGCACCTGC  
CAGGAGAACAGGCAGTGGCATGGTGGATCCAGACATGATCAAAGCCATCAACCAGGGCAA  
CTATGGCTGGCAGGCTGGGAACCACAGCGCCTTCTGGGGCATGACCCTGGATGAAGGCAT  
TCGCTACCGCCTGGGCACCATCCGCCCATCTTCCTCGGTTCATGAACATGCATGAAATTTA  
TACAGTGCTGAACCCAGGGGAGGTGCTTCCCACAGCCTTCGAGGCCTCTGAGAAGTGGCC  
CAACCTGATTCATGAGCCTCTTGACCAAGGCAACTGTGCAGGCTCCTGGGCCTTCTCCAC  
AGCAGCTGTGGCATCCGATCGTGTCTCAATCCATTCTCTGGGACACATGACGCCTGTCTT  
GTGCCCCCAGAACCTGTGTCTTGTGACACCCACCAGCAGCAGGGCTGCCGCGGTGGGCG  
TCTCGATGGTGCCTGGTGGTTCTTGCCTGCGCGAGGGGTGGTGTCTGACCACTGCTACCC  
CTTCTCGGGCCGTGAACGAGACGAGGCTGGCCCTGCGCCCCCTGTATGATGCACAGCCG  
AGCCATGGGTTCGGGGCAAGCGCCAGGCCACTGCCCACTGCCCAACAGCTATGTTAATAA  
CAATGACATCTACCAGGTCACCTCTGTCTACCGCCTCGGCTCCAACGACAAGGAGATCAT  
GAAGGAGCTGATGGAGAATGGCCCTGTCCAAGCCCTCATGGAGGTGCATGAGGACTTCTT  
CCTATACAAGGGAGGCATCTACAGCCACACGCCAGTGAGCCTTGGGAGGCCAGAGAGATA  
CCGCCGGCATGGGACCCACTCAGTCAAGATCACAGGATGGGGAGAGGAGACGCTGCCAGA  
TGGAAGGACGCTCAAATACTGGACTGCGGCCAACTCCTGGGGCCCAGCCTGGGGCGAGAG  
GGGCCACTTCCGCATCGTGCGCGGCGTCAATGAGTGCACATCGAGAGCTTCGTGCTGGG  
CGTCTGGGGCCGCGTGGGCATGGAGGACATGGGTTCATCACTGAGGCTGCGGGCACCACGC  
GGGGTCCGGCCTGGGATCCAGGCTAAGGGCCGGCGGAAGAGGCCCAATGGGGCGGGTGAC  
CCCAGCCTCGCCCGACAGAGCCCGGGCGCAGGCGGGCGCCAGGGCGCTAATCCCGGCGC  
GGGTTCCGCTGACGACGCGCCCCGCTGGGAGCCGCGGGCAGGCGAGACTGGCGGAGCCC  
CCAGACCTCCCAGTGGGGACGGGGCAGGGCCTGGCCTGGGAAGAGCACAGCTGCAGATCC  
CAGGCCTCTGGCGCCCCCACTCAAGACTACCAAAGCCAGGACACCTCAAGTCTCCAGCCC  
CAATACCCCAACCCCAATCCCGTATTCTTTTTTTTTTTTTTTTAGACAGGGTCTTGCTCCG  
TTGCCCAGGTTGGAGTGCAGTGGCCCATCAGGGCTCACTGTAACCTCCGACTCCTGGGTT  
CAAGTGACCCTCCACCTCAGCCTCTCAAGTAGCTGGGACTACAGGTGCACCACCACACC  
TGGCTAATTTTTTGTATTTTTTGTAAGAGGGGGGTCTCACTGTGTTGCCCAGGCTGGTTT  
CGAACTCCTGGGCTCAAGCGGTCCACCTGCCTCCGCCTCCCAAAGTGCTGGGATTGCAGG  
CATGAGCCACTGCACCCAGCCCTGTATTCTTATTCTTCAGATATTTATTTTTCTTTTCAC  
TGTTTTTAAATAAAACCAAAGTATTGATAAAAAAAA

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**FIGURE 26**

MWRCPLGLLLLLPLAGHLALGAQQGRGRRELAPGLHLRGIRDAGGRYCQEQLCCRGRAD  
DCALPYLGAICYCDLFCNRTVSDCCPDFWDFCLGVPPPPFPIQGCMHGGRIYPVLGTYWD  
NCNRCTCQENRQWHGGSRHDQSHQPGQLWLAGWEPQRLLGHDPG

**N-glycosylation site:**

amino acids 78-82, 161-165

**Casein kinase II phosphorylation site:**

amino acids 80-84, 117-121, 126-130, 169-173, 205-209, 296-300,  
411-415

**N-myristoylation site:**

amino acids 21-27, 39-45, 44-50, 104-110, 160-164, 224-230,  
269-275, 378-384, 442-448

**Amidation site:**

amino acids 26-30, 318-322

**Eukaryotic thiol (cysteine) proteases histidine active site:**

amino acids 398-409

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**FIGURE 27**

CCCACGCGTCCGGCAGGTTTTTCTTCAAGCCAAGAAGGACACGGATTGGCTGAAGGAGAA  
AGTGCAGAGCTTGCAGACACTGGCTGCCAACAACTCTGCGTTGGCCAAAGCCAACAACGA  
CACCTTGGAGGATATGAACAGCCAGCTCAACTCATTACAGGTCAGATGGAGAACATCAC  
CACTATCTCTCAAGCCAACGAGCAGAACCTGAAAGACCTGCAGGACTTACACAAAGATGC  
AGAGAATAGAACAGCCATCAAGTTCAACCAACTGGAGGAACGCTTCCAGCTCTTTGAGAC  
GGATATTGTGAACATCATTAGCAATATCAGTTACACAGCCCACCACCTGCGGACGCTGAC  
CAGCAATCTAAATGAAGTCAGGACCACCTTGCACAGATACCTTACCAAACACACAGATGAT  
CTGACCTCCTTGAATAATACCCTGGCCAACATCCGTTTGGATTCTGTTTCTCTCAGGATG  
CAACAAGATTTGATGAGGTGAGGTTAGACACTGAAGTAGCCAACCTTATCAGTGATTATG  
GAAGAAATGAAGCTAGTAGACTCCAAGCATGGTCAGCTCATCAAGAATTTTACAATACTA  
CAAGGTCCACCGGGCCCCAGGGGTCCAAGAGGTGACAGAGGATCCCAGGGACCCCTGGC  
CCAACTGGCAACAAGGGACAGAAAGGAGAGAAGGGGGAGCCTGGACCACCTGGCCCTGCG  
GGTGAGAGAGGCCCAATTGGACCAGCTGGTCCCCCGGAGAGCGTGGCGGCAAAGGATCT  
AAAGGCTCCCAGGGCCCCAAAGGCTCCCGTGGTTCCCTGGGAAGCCCGGCCCTCAGGGC  
CCCAGTGGGGACCCAGGCCCCCGGGCCACCAGGCAAAGAGGGACTCCCCGGCCCTCAG  
GGCCCTCCTGGCTTCCAGGGACTTCAGGGCACCGTTGGGGAGCCTGGGGTGCTTGACCT  
CGGGGACTGCCAGGCTTGCTTGGGGTACCAGGCATGCCAGGCCCAAGGGCCCCCGGC  
CCTCCTGGCCCATCAGGAGCGGTGGTGGCCCTGGCCCTGCAGAATGAGCCAACCCCGGCA  
CCGGAGGACAATAGCTGCCCCGCTCACTGGAAGAACTTCACAGACAAATGCTACTATTTT  
TCAGTTGAGAAAGAAATTTTGGAGGATGCAAAGCTTTTCTGTGAAGACAAGTCTTCACAT  
CTTGTTTTTCATAAACACTAGAGAGGAACAGCAATGGATAAAAAAACAGATGGTAGGGAGA  
GAGAGCCACTGGATCGGCCTCACAGACTCAGAGCGTGAAAATGAATGGAAGTGGCTGGAT  
GGGACATCTCCAGACTACAAAAATTGGAAAGCTGGACAGCCGGATAACTGGGGTCATGGC  
CATGGGCCAGGAGAAGACTGTGCTGGGTTGATTTATGCTGGGCAGTGGAACGATTTCCAA  
TGTGAAGACGTCAATAACTTCATTTGCGAAAAAGACAGGGAGACAGTACTGTCATCTGCA  
TTATAACGGACTGTGATGGGATCACATGAGCAAATTTTCAGCTCTCAAAGGCAAAGGACA  
CTCCTTTCTAATTGCATCACCTTCTCATCAGATTGAAAAAAAAAAGCACTGAAAACCAA  
TACTGAAAAAAAAATTGACAGCTAGTGTTTTTTTACCATCCGTCATTACCCAAAGACTTGG  
GAACTAAAATGTTCCCCAGGGTGATATGCTGATTTTCATTGTGCACATGGACTGAATCAC  
ATAGATTCTCCTCCGTCAGTAACCGTGCGATTATACAAATTATGTCTTCCAAAGTATGGA  
ACACTCCAATCAGAAAAAGGTTATCATTGGTCGTTGAGTTATGGGAAGAACTTAAGCATA  
TACTGTGTAAACAGTGCCATACATTTCTAAAATCCCAAGTGTAGGAAAAATATGCAGACA  
TACAGATATATAGGCCAACTATTAGTAATAATATGAAATATACTTAAAGAGCTTTTAAAA  
CTTTGTATTTTTTGTACAAAAAAA

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**FIGURE 28**

MQQDLMRSLDTEVANLSVIMEEMKLVD SKHGQLIKNFTILQGPPGPRGPRGDRGSQGPP  
GPTGNKGQKGEKGEPPGPAGERGPAGPPGERGGKSGSKGSQGPKGSRGSPGKPGPQ  
GPSGDPGPPGPPGKEGLPGPQGPFGQLQGTVEPGVPGPRGLPGLPGVPGMPGPKGPP  
GPPGPSGAVVPLALQNEPTPAPEDNSCPHWNFTDKCYYFSVEKEIFEDAKLFCEDKSS  
HLVFINTREEQQWIKKQMVGRESHWIGLTDSERENEWKWLDGTSPDYKNWKAGQPDNWDH  
GHGPGEDCAGLIYAGQWDFQCEDVNNFICEKDRETVLSSAL

**Signal sequence:**

None

**Transmembrane domain:**

None

**N-glycosylation site:**

16-19, 37-40, 213-216

**Tyrosine kinase phosphorylation site:**

212-220

**N-myristoylation site:**

97-102, 100-105, 148-153, 267-272, 293-298, 310-315

**Cell attachment sequence:**

51-53

**C-type lectin domain signature:**

308-330

**Lectin C-type domain:**

233-330

**Collagen triple helix repeat:**

43-102, 127-186

**FIGURE 29**

GGACTAATCTGTGGGAGCAGTTTATTCAGTATCACCCAGGGTGCAGCCACACCAGGACT  
GTGTTGAAGGGTGTTTTTTTCTTTTAAATGTAATACCTCCTCATCTTTTCTTCTTACAC  
AGTGTCTGAGAACATTTACATTATAGATAAGTAGTACATGGTGGATAAATTCTACTTTTA  
GGAGGACTACTCTCTTCTGACAGTCTTAGACTGGTCTTCTACACTAAGACACCATGAAGG  
AGTATGTGCTCCTATTATTCTCTGGCTTTGTGCTCTGCCAAACCCTTCTTTAGCCCTTAC  
ACATCGCACTGAAGAATATGATGCTGAAGGATATGGAAGACACAGATGATGATGATGATG  
ATGATGATGATGATGATGATGATGAGGACAACCTCTCTTTTTTCCAACAAGAGAGCCAAGAA  
GCCATTTTTTTTCCATTTGATCTGTTTCCAATGTGTCCATTTGGATGTCAGTGCTATTCA  
GAGTTGTACATTGCTCAGATTTAGGTTTGACCTCAGTCCCAACCAACATTCCATTTGATA  
CTCGAATGCTTGATCTTCAAAACAATAAAATTAAGGAAATCAAAGAAAATGATTTTAAAG  
GACTCACTTCACTTTATGGTCTGATCCTGAACAACAACAAGCTAACGAAGATTCACCCAA  
AAGCCTTTCTAACCACAAAGAAGTTGCGAAGGCTGTATCTGTCCCACAATCAACTAAGTG  
AAATACCACTTAATCTTCCCAAATCATTAGCAGAACTCAGAATTATGAAAAATAAAGTTA  
AGAAAAATACAAAAGGACACATTCAAAGGAATGAATGCTTTACACGTTTTTGAAAATGAGTG  
CAAACCCCTCTTGATAATAATGGGATAGAGCCAGGGGCATTTGAAGGGGTGACGGTGTTCC  
ATATCAGAATTGCAGAAGCAAACCTGACCTCAGTTCCTAAAGGCTTACCACCAACTTTAT  
TGGAGCTTCACTTAGATTATAATAAAATTTCAACAGTGGAACCTTGAGGATTTTAAACGAT  
ACAAAGAATAACAAAGGCTGGGCCTAGGAAACAACAAAATCACAGATATCGAAAATGGGA  
GTCTTGCTAACATACCACGTGTGAGAGAAATACATTTGGAAAAACAATAAACTAAAAA  
TCCCTTCAGGATTACCAGAGTTGAAATACCTCCAGATAATCTTCCTTCATTCTAATTCAA  
TTGCAAGAGTGGGAGTAAATGACTTCTGTCCAACAGTGCCAAAGATGAAGAAATCTTTAT  
ACAGTGCAATAAGTTTATTCAACAACCCGGTGAAATACTGGGAAATGCAACCTGCAACAT  
TTCGTTGTGTTTTGAGCAGAATGAGTGTTTCAGCTTGGGAACCTTTGGAATGTAATAATTAG  
TAATTGGTAATGTCCATTTAATATAAGATTCAAAAATCCCTACATTTGGAATACTTGAAC  
TCTATTAATAATGGTAGTATTATATATACAAGCAAATATCTATTCTCAAGTGGTAAGTCC  
ACTGACTTATTTTATGACAAGAAATTTCAACGGAATTTTGCCAAACTATTGATACATAAG  
GGGTTGAGAGAAACAAGCATCTATTGCAGTTTTCTTTTTTGCGTACAAATGATCTTACATA  
AATCTCATGCTTGACCATTCTTTCTTCATAACAAAAAAGTAAGATATTCGGTATTTAAG  
ACTTTGTATCAAGCACATTTTAAAAAGAACTGTACTGTAAATGGAATGCTTGACTTAGC  
AAAATTTGTGCTCTTTCATTTGCTGTTAGAAAAACAGAATTAACAAAAGACAGTAATGTGA  
AGAGTGCAATTACACTATTCTTATTCTTTAGTAACTTGGGTAGTACTGTAATATTTTTTAAT  
CATCTTAAAGTATGATTTGATATAATCTTATTGAAATTACCTTATCATGTCTTAGAGCCC  
GTCTTTATGTTTTAAACTAATTTCTTAAATAAAGCCTTCAGTAAATGTTTATTACCAAC  
TTGATAAATGCTACTCATAAGAGCTGGTTTTGGGGCTATAGCATATGCTTTTTTTTTTTTT  
ATTATTACCTGATTTAAAAATCTCTGTAAAAACGTGTAGTGTTCATAAAATCTGTAACT  
CGCATTTTAAATGATCCGCTATTATAAGCTTTTAAATAGCATGAAAATTGTTAGGCTATATA  
ACATTGCCACTTCAACTCTAAGGAATATTTTTGAGATATCCCTTTGGAAGACCTTGCTTG  
GAAGAGCCTGGACACTAAACAATTCTACACCAAATTGTCTCTTCAAATACGTATGGACTGG  
ATAACTCTGAGAAACACATCTAGTATAACTGAATAAGCAGAGCATCAAATTTAAACAGACA  
GAAACCGAAAGCTCTATATAAATGCTCAGAGTTCTTTATGTATTTCTTATTGGCATTCAA  
CATATGTAAATCAGAAAACAGGGAAATTTTCATTAAAAATATTGGTTTTGAAAT



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**FIGURE 30**

MKEYVLLLLFLALCSAKPFFSPSHIALKNMMLKDMEDTDDDDDDDDDDDDDDDEDNSLFPTRE  
PRSHFFPFDLFPMCPFGCQCYSRVVHCSDLGLTSVPTNIPFDTRMLDLQNNKIKEIKEND  
FKGLTSLYGLILNNNKLTKIHPKAFLTTKKLRRLYL SHNQLSEIPLNLPKSLAELRIHEN  
KVKKIQKDTFKGMNALHVLEMSANPLDNNGIEPGA FEGVTVPHIRIAEAKLTSVPGKGLPP  
TLLELHLDYNKISTVELEDFKRYKELQRLGLGNNKITDIENGLANI PRVREIHLENNKL  
KKIPSGLPPELKYLQIIFLHSNSIARVGVNDFCPTVPKMKKSLYSAISLFNNPVKYWEMQP  
ATFRCVLSRMSVQLGNFGM

**Signal sequence:**  
amino acids 1-15

**N-glycosylation site:**  
amino acids 281-285

**N-myristoylation sites:**  
amino acids 129-135, 210-216, 214-220, 237-243, 270-276,  
282-288

**Leucine zipper pattern:**  
amino acids 154-176

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**FIGURE 31**

AGCAGGGAAATCCGGATGTCTCGGTTATGAAGTGGAGCAGTGAGTGTGAGCCTCAACATA  
GTTCCAGAACTCTCCATCCGGACTAGTTATTGAGCATCTGCCTCTCATATCACCAGTGGC  
CATCTGAGGTGTTTTCCCTGGCTCTGAAGGGGTAGGCACGATGGCCAGGTGCTTCAGCCTG  
GTGTTGCTTCTCACTTCCATCTGGACCACGAGGCTCCTGGTCCAAGGCTCTTTGCGTGCA  
GAAGAGCTTTCCATCCAGGTGTCATGCAGAATTATGGGGATCACCCCTTGTGAGCAAAAAG  
GCCAACCAGCAGCTGAATTTACAGAAGCTAAGGAGGCCTGTAGGCTGCTGGGACTAAGT  
TTGGCCGGCAAGGACCAAGTTGAAACAGCCTTGAAAGCTAGCTTTGAAACTTGCAGCTAT  
GGCTGGGTTGGAGATGGATTTCGTGGTCACTCTTAGGATTAGCCCAAACCCCAAGTGTGGG  
AAAAATGGGGTGGGTGTCTGATTTGGAAGGTTCCAGTGAGCCGACAGTTTGCAGCCTAT  
TGTTACAACTCATCTGATACTTGGACTAACTCGTGCATTCCAGAAATTATCACCACCAAA  
GATCCCATATTCAACACTCAAACTGCAACACAAACAAGAAATTTATTGTCACTGACAGT  
ACCTACTCGGTGGCATCCCCCTTACTCTACAATACCTGCCCCCTACTACTCCTCCTGCT  
CCAGCTTCCACTTCTATTCCACGGAGAAAAAATTGATTTGTGTACAGAAAGTTTTTATG  
GAACTAGCACCATGTCTACAGAACTGAACCATTGTGTTGAAAATAAAGCAGCATTCAAG  
AATGAAGCTGCTGGGTTTGGAGGTGTCCCCACGGCTCTGCTAGTGCTTGCTCTCCTCTTC  
TTTGCTGCTGCAGCTGGTCTTGGATTTTGTCTATGTCAAAAGGTATGTGAAGGCCCTTCCCT  
TTTACAAACAAGAAATCAGCAGAAGGAAATGATCGAAACCAAAGTAGTAAAGGAGGAGAAG  
GCCAATGATAGCAACCCTAATGAGGAATCAAAGAAAACCTGATAAAAACCCAGAAGAGTCC  
AAGAGTCCAAGCAAACTACCGTGCGATGCCTGGAAGCTGAAGTTTAGATGAGACAGAAA  
TGAGGAGACACACCTGAGGCTGGTTTTCTTTCATGCTCCTTACCCTGCCCCAGCTGGGGAA  
ATCAAAAGGGCCAAAGAACCAAGAAGAAAGTCCACCCTTGGTTCTTAAGTGAATCAGC  
TCAGGACTGCCATTGGACTATGGAGTGCACCAAAGAGAATGCCCTTCTCCTTATTGTAAC  
CCTGTCTGGATCCTATCCTCCTACCTCCAAAGCTTCCCACGGCCTTCTAGCCTGGCTAT  
GTCCTAATAATATCCCACTGGGAGAAAGGAGTTTTTGCAAAGTGCAAGGACCTAAACATC  
TCATCAGTATCCAGTGGTAAAAAGGCCTCCTGGCTGTCTGAGGCTAGGTGGGTTGAAAGC  
CAAGGAGTCACTGAGACCAAGGCTTCTCTACTGATTCCGCAGCTCAGACCCCTTCTTCA  
GCTCTGAAAGAGAAACACGTATCCACCTGACATGTCCTTCTGAGCCCGGTAAGAGCAAA  
AGAATGGCAGAAAAGTTTAGCCCCTGAAAGCCATGGAGATTCTCATAACTTGAGACCTAA  
TCTCTGTAAAGCTAAAAATAAGAAATAGAACAAGGCTGAGGATACGACAGTACACTGTCA  
GCAGGGACTGTAAACACAGACAGGGTCAAAGTGTCTTCTCTGAACACATTGAGTTGGAAT  
CACTGTTTAGAACACACACACTTACTTTTTCTGGTCTCTACCACTGCTGATATTTCTCT  
AGGAAATATACTTTTACAAGTAACAAAAATAAAACTCTTATAAATTCTATTTTTATCT  
GAGTTACAGAAATGATTACTAAGGAAGATTACTCAGTAATTTGTTTAAAAGTAATAAAA  
TTCAACAAACATTTGCTGAATAGCTACTATATGTCAAGTGTGTGCAAGGTATTACACTC  
TGTAATTGAATATTATTCTCAAAAAATTGCACATAGTAGAACGCTATCTGGGAAGCTAT  
TTTTTTCAGTTTTGATATTTCTAGCTTATCTACTTCCAAACTAATTTTTATTATTGCTGA  
GACTAATCTTATTCATTTTCTCTAATATGGCAACCATTATAACCTTAATTTATTATTAAC  
ATACCTAAGAAGTACATTGTTACCTCTATATACCAAAGCACATTTTAAAAGTGCCATTAA  
CAAATGTATCACTAGCCCTCCTTTTTCCAACAAGAAGGGACTGAGAGATGCAGAAATATT  
TGTGACAAAAAATTAAAGCATTTAGAAAACCT

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**FIGURE 32**

MARCFSLVLLLLTSIWTTTRLLVQGSRLAEELSIQVSCRIMGITLVSKKANQQLNFTEAKEA  
CRLGLSLAGKDQVETALKASFETCSYGWVGDFVVISRISPNPKCGKNGVGVLWKPVP  
SRQFAAYCYNSSDTWTNSCIPEIITTKDPIFNTQTATQTTEFIVSDSTYSVASPYSTIPA  
PTTTPPAPASTSIPRRKKLICVTEVFMETSTMSTETEPFVENKAAFKNEAAGFGGVPTAL  
LVLALLFFGAAAGLGFCYVKRYVKAFPFNTKNQKEMIETKVVKEEKANDSNPNEESKKT  
DKNPEESKSPSKTTVRCLEAEV

**Signal sequence:**

amino acids 1-16

**Transmembrane domain:**

amino acids 235-254

**N-glycosylation site:**

amino acids 53-57, 130-134, 289-293

**Casein kinase II phosphorylation site:**

amino acids 145-149, 214-218

**Tyrosine kinase phosphorylation site:**

amino acids 79-88

**N-myristoylation site:**

amino acids 23-29, 65-71, 234-240, 235-239, 249-255, 253-259

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**FIGURE 33**

GAAATAAAAAAAAAAGGGAAGCAAGCTTAGCTGTACACACCTGAGTCTTGCAAAAAGCTGACG  
 CCCCACCCAGGAGCAGGGTGGTGGCTGGGGCGATGGTGGACGCCCTGAAGATGTCCCATG  
 GCTACTGAAGGGGCTGCCAGTTAGGGAACAGAGTGGCGGGCATGGTGTGTAGCCTATGG  
 GTGCTGCTCCTGGTGTCTTCAGTTCTGGCTCTGGAAGAGGTATTGCTGGACACCACCGGA  
 GAGACATCTGAGATTGGCTGGCTCACCTACCCACCAGGGGGGTGGGACGAGGTGAGTGT  
 CTGGACGACCAGCGACGCCCTGACTCGGACCTTTGAGGCATGTTCATGTGGCAGGGGCCCT  
 CCAGGCACCGGGCAGGACAATTGGTTGCAGACACACTTTGTGGAGCGCGCGGGGCCAG  
 AGGGCGCACATTCGACTCCACTTCTCTGTGCGGCATGCTCCAGCCTGGGTGTGAGCGGG  
 GGCACCTGCCGGGAGACCTTCACCCCTTTACTACCGTCAGGCTGAGGAGCCCGACAGCCCT  
 GACAGCGTTTTCTCCTGGCACCTCAAACGTTGGACCAAGGTGGACACAATTGCAGCAGAC  
 GAGAGCTTTCCATCCTCCTCCTCCTCCTCCTCCTCCTCCTCCTCCTCCTCCTCCTCCTCCT  
 GTGGGACCCACGGGGCTGGGCAGCGGGCTGGACTGCAACTGAACGTCAAAGAGCGGAGC  
 TTTGGGCCTCTCACCCAAACGCGGCTTCTACGTGGCCTTCCAGGACACGGGGGCTGCCTG  
 GCCCTGGTTCGCTGTACGGCTCTTCTCCTACACCTGCCCTGCCGTGCTCCGATCCTTTGCT  
 TCCTTTCCAGAGACGCAGGCCAGTGGGGCTGGGGGGGCTCCCTGGTGGCAGCTGTGGGC  
 ACCTGTGTGGCTCATGCAGAGCCAGAGGAGGATGGAGTAGGGGGCCAGGCAGGAGGCAGC  
 CCCCCAGGCTGCACTGCAACGGGGAGGGCAAGTGGATGGTAGCTGTGGGGGCTGCCGC  
 TGCCAGCCTGGATACCAACCAGCACGAGGAGACAAGGCCTGCCAAGCCTGCCACGGGGG  
 CTCTATAAGGCTTCTGCTGGGAATGCTCCCTGCTCACCATGCCCTGCCCGCAGTCACGCT  
 CCAACCCAGCAGCCCCGTTTTGCCCTGCCTGGAGGGCTTCTACCGGGCCAGTTCGGAC  
 CCACCAGAGGCCCCCTGCACTGGTCTCCATCGGCTCCCCAGGAGCTTTGGTTTGAGGTG  
 CAAGGCTCAGCACTCATGCTACACTGGCGCCTGCCCTCGGGAGCTGGGGGGTTCGAGGGGAC  
 CTGCTCTTCAATGTGCTGTGCAAGGAGTGTGAAGGCCGCCAGGAACCTGCCAGCGGTGGT  
 GGGGGCACTTGTACCGCTGCAGGGATGAGGTCCACTTCGACCCTGCCAGAGAGGCCTG  
 ACTGAGAGCCGAGTGTAGTGGGGGGACTCCGGGCACACGTACCCTACATCTTAGAGGTG  
 CAGGCTGTTAATGGGGTGTCTGAGCTCAGCCCTGACCCTCCTCAGGCTGCAGCCATCAAT  
 GTCAGCACCAGCCATGAAGTGCCCTCTGCTGTCCCTGTGGTGCACCAGGTGAGCCGGGCA  
 TCCAACAGCATCACGGTGTCTGGCCGCAGCCCGACCAGACCAATGGGAACATCCTGGAC  
 TATCAGCTCCGCTACTATGACCAGGCAGAAGACGAATCCCACTCCTTCACCCTGACCAGC  
 GAGACCAACACTGCCACCGTGACACAGCTGAGCCCTGGCCACATCTATGGTTTTCCAGGTG  
 CGGGCCCGGACTGCTGCCGGCCACGGCCCCCTACGGGGGCAAAGTCTATTTCCAGACACTT  
 CCTCAAGGGGAGCTGTCTTCCAGCTTCCGAAAGACTCTCCTTGGTGATCGGCTCCACC  
 CTGGGGGCTTTGGCCTTCTCCTGCTGGCAGCCATCACCGTGCTGGCGGTGCTCTTCCAG  
 CGGAAGCGGCGTGGGACTGGCTACACGGAGCAGCTGCAGCAATACAGCAGCCAGGACTC  
 GGGGTGAAGTATTACATCGACCCCTCCACCTACGAGGACCCCTGTAGGCCATCCGAGAA  
 CTTGCCCGGGAAGTCGATCCTGCTTATATCAAGATTGAGGAGGTATTGGGACAGGCTCT  
 TTTGGAGAAGTGCGCCAGGGCCGCCTGCAGCCACGGGGACGGAGGGAGCAGACTGTGGCC  
 ATCCAGGCCCTGTGGGCGGGGGCGCCGAAAGCCTGCAGATGACCTTCTGGGCCGGGCC  
 GCAGTGCTGGGTGAGTTCCAGCACCCCAACATCCTGCGGCTGGAGGGCGTGGTCACCAAG  
 AGCCGACCCCTCATGGTGCTGACGGAGTTCATGGAGCTTGGCCCCCTGGACAGCTTCCTC  
 AGGCAGCGGGAGGGCCAGTTCAGCAGCCTGCAGCTGGTGGCCATGCAGCGGGGAGTGGCT  
 GCTGCCATGCAGTACCTGTCCAGCTTTGCCTTCGTCCATCGCTCGCTGTCTGCCACAGC  
 GTGCTGGTGAATAGCCACTTGGTGTGCAAGGTGGCCCGTCTTGGCCACAGTCTCAGGGC  
 CCAAGTTGTTTGCTTCGCTGGGCAGCCCCAGAGGTCAATTGCACATGGAAAGCATACTCAT  
 GTGGGAAGTGATGAGTTATGGAGAACGGCCTTACTGGGACATGAGTGAAGCAGGAGGTACT  
 AAATGCAATAGAGCAGGAGTTCCGGCTGCCCGCCCTCCAGGCTGTCTCCTGGATTACA

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TCTACTTATGTTGGACACTTGGCAGAAGGACCGTGCCCGGCGGCCTCATTTTGACCAGCT  
GGTGGCTGCATTTGACAAGATGATCCGCAAGCCAGATACCCTGCAGGCTGGCGGGGACCC  
AGGGGAAAGGCCTTCCCAGGCCCTTCTGACCCCTGTGGCCCTGGACTTTCCTTGTCTGGA  
CTCACCCCAGGCCTGGCTTTCAGCCATTGGACTGGAGTGCTACCAGGACAACCTTCTCCAA  
GTTTGGCCTCTGTACCTTCAGTGATGTGGCTCAGCTCAGCCTAGAAGACCTGCCTGCCCT  
GGGCATCACCCCTGGCTGGCCACCAGAAGAAGCTGCTGCACCACATCCAGCTCCTTCAGCA  
ACACCTGAGGCAGCAGGGCTCAGTGGAGGTCTGAGAATGACGATACCCGTGACTCAGCCC  
TGGACACTGGTCCGAGAAGGGACATGTGGGACGTGAGCCGGGCTCCAACAGCCTCTGTGA  
GAGATGCCCCACACCAAACCAACCCTCCGATGGCTGCATTCCCTGGTCCTCCGCTTTTC  
CACCAGCCCCCTCCTCATTAAGGGAAAGAAGGGAATTTGCAAAAAAAAAAAAAAAAAAAAA  
AAAAAA

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**FIGURE 34**

MATEGAAQLGNRVAGMVCSLWVLLLSSVLALVEVLLDTTGETSEIGWLTYPPGGWDEV  
VLDDQRRLTRTFEACHVAGAPPGTGQDNWLQTHFVERRGAQRAHIRLHFSVRACSSSLGVS  
GGTCRETFTLYYRQAEEDSPDSVSSWHLKRWTQVDTIAADESFSSSSSSSSSSSSSSAAW  
AVGPHGAGQAGLQNLVKERSFGPLTQRGFYVAFQDTGACLALVAVRLFSYTCPAVLRSF  
ASFPEAQASGAGGASLVAAGVTCVAHAPEEDGVGGQAGGSPRLHCNNEGKWMVAVGGC  
RCQPGYQPARGDKACQACPRGLYKASAGNAPCSPCPARSHAPNPAAPVPCPCLEGFYRASS  
DPPEAPCTGPPSAPQELWFEVQGSALMLHWRLPRELGGRGDLLFNVCKECEGRQEPASG  
GGGTCHRCRDEVHFDPRQRGLTESRVLVGGLRAHVPILEVQAVNGVSELSPDPPQAAAI  
NVSTSEHVPSAVPVVHVQVSRASNSITVSWPQPDQTNGNILDYQLRYDQAEDESHSFTLT  
SETNTATVTQLSPGHIYGFQVRARTAAGHGPGYGGKVYFQTLPPQELSSQLPERLSLVIGS  
TLGALAFLLLLAAITVLAVVFQRKRRTGYTEQLQQYSSPGLGVKYYIDPSTYEDPCQAIR  
ELAREVDPAYIKIEEVIGTGSFGEVRQGRQLQPRGRREQTVAIQALWAGGAESLQMTFLGR  
AAVLGQFQHPNLRLEGVVTKSRPLMVLTEFMELGPLDSFLRQREGQFSSLQLVAMQRGV  
AAAMQYLSSFAFVHRSLSAHSVLVNSHLVCKVARLGHSPQGPSCLLRWAAPEVIAHGKHT  
HVGSDDELWRTALLGHE

**signal sequence:**

Amino acids 1-31

**Transmembrane domains:**

Amino acids 217-234;598-618

**N-glycosylation site:**

Amino acids 481-485

**Glycosaminoglycan attachment sites:**

Amino acids 249-253;419-423

**cAMP- and cGMP-dependent protein kinase phosphorylation sites:**

Amino acids 66-70;150-154;624-628

**Tyrosine kinase phosphorylation sites:**

Amino acids 644-673;664-671

**N-myristoylation sites:**

Amino acids 10-16;15-21;79-85;99-105;118-124;188-194;  
192-198;218-224;250-256;261-267;275-281;276-282;298-304;321-  
327;328-334;420-426;421-427;440-446;449-455;599-605;626-632;  
708-714;766-772;779-785

**Amidation site:**

Amino acids 693-697

**Cell attachment sequences:**

Amino acids 310-313;399-402

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**FIGURE 35**

GGGGTCTCCCTCAGGGCCGGGAGGCACAGCGGTCCCTGCTTGCTGAAGGGCTGGATGTAC  
GCATCCGCAGGTTCCCGCGGACTTGGGGGCGCCCGCTGAGCCCCGGCGCCCGCAGAAGAC  
TTGTGTTTGCCCTCCTGCAGCCTCAACCCGGAGGGCAGCGAGGGCCTACCACCATGATCAC  
TGGTGTGTTT CAGCATGCGCTTGTGGACCCAGTGGGCGTCCTGACCTCGCTGGCGTACTG  
CCTGCACCAGCGGCGGGTGGCCCTGGCCGAGCTGCAGGAGGCCGATGGCCAGTGTCCGGT  
CGACCGCAGCCTGCTGAAGTTGAAAATGGTGCAGGTCGTGTTTCGACACGGGGCTCGGAG  
TCCTCTCAAGCCGCTCCCGCTGGAGGAGCAGGTAGAGTGGAACCCCGAGCTATTAGAGGT  
CCCACCCCAAACCTCAGTTTGATTACACAGTCACCAATCTAGCTGGTGGTCCGAAACCATA  
TTCTCCTTACGACTCTCAATACCATGAGACCACCCTGAAGGGGGGCATGTTTGCTGGGCA  
GCTGACCAAGGTGGGCATGCAGCAAATGTTTGCCCTTGGGAGAGAGACTGAGGAAGAACTA  
TGTGGAAGACATTCCCTTCTTTCACCAACCTTCAACCCACAGGAGGTCTTTATTCTGTTT  
CACTAACATTTTTTCGGAATCTGGAGTCCACCCGTTGTTTGCTGGCTGGGCTTTTTCCAGTG  
TCAGAAAGAAGGACCCATCATCATCCACACTGATGAAGCAGATT CAGAAGTCTTGTATCC  
CAACTACCAAAGCTGCTGGAGCCTGAGGCAGAGAACCAGAGGCCGGAGGCAGACTGCCTC  
TTTACAGCCAGGAATCTCAGAGGATTTGAAAAAGGTGAAGGACAGGATGGGCATTGACAG  
TAGTGATAAAGTGGACTTCTTCATCCTCCTGGACAACGTGGCTGCCGAGCAGGCACACAA  
CCTCCCAAGCTGCCCCATGCTGAAGAGATTTGCACGGATGATCGAACAGAGAGCTGTGGA  
CACATCCTTGTAATACTGCCCAAGGAAGACAGGGAAAGTCTTCAGATGGCAGTAGGCC  
ATTCCTCCACATCCTAGAGAGCAACCTGCTGAAAGCCATGGACTCTGCCACTGCCCCCGA  
CAAGATCAGAAAGCTGTATCTCTATGCGGCTCATGATGTGACCTTCATACCGCTCTTAAT  
GACCTGGGGATTTTTGACCACAAATGGCCACCGTTTGCTGTTGACCTGACCATGGAACT  
TTACCAGCACCTGGAATCTAAGGAGTGGTTTGTGTCAGCTCTATTACCACGGGAAGGAGCA  
GGTGCCGAGAGGTTGCCCTGATGGGCTCTGCCCGCTGGACATGTTCTTGAATGCCATGTC  
AGTTTATACCTTAAGCCAGAAAAATACCATGCACTCTGCTCTCAAACCTCAGGTGATGGA  
AGTTGGAATGAAGAGTAACTGATTTATAAAAGCAGGATGTGTTGATTTTAAATAAAGT  
GCCTTTATACAATG

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**FIGURE 36**

MITGVFSMRLWTPVGVLTSLAYCLHQRRVALAELQEQADGQCPVDRSLLKLKMVQVVFRHG  
ARSPLKPLPLEEQVEWNPQLLEVPPQTQFDYTVTNLAGGPKPYSPYDSQYHETTLKGGMF  
AGQLTKVGMQMFALGERLRKNYVEDIPFLSPTFNPQEVFIRSTNIFRNLESTRCLLAGL  
FQCQKEGP IIIHTDEADSEVLYPNYQSCWSLRQRTGRRTASLQPGISED LKKVKDRMG  
IDSSDKVDFFILLDNVAAEQAHNLPSCPMLKRFARMIEQRAVDTSLYILPKEDRESLQMA  
VGPFLLHILES NLLKAMDSATAPDKIRKLYLYAAHDVTFIPLLMTLGIFDHKWPPFAVDLT  
MELYQHLESKEWFVQLYYHGKEQVPRGCPDGLCPLDMFLNAMS VYTLSPEKYHALCSQTQ  
VMEVGNEE

**Signal sequence:**

amino acids 1-23

**cAMP- and cGMP-dependent protein kinase phosphorylation site:**

amino acids 218-222

**Casein kinase II phosphorylation site:**

amino acids 87-91, 104-108, 320-324

**Tyrosine kinase phosphorylation site:**

amino acids 280-288

**N-myristoylation site:**

amino acids 15-21, 117-123, 118-124, 179-185, 240-246, 387-393

**Amidation site:**

amino acids 216-220

**Leucine zipper pattern:**

amino acids 10-32

**Histidine acid phosphatases phosphohistidine signature:**

amino acids 50-65



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**FIGURE 37**

ACTGCACTCGGTTCTATCGATTGAATTCCCCGGGGATCCTCTAGAGATCCCTCGACCTCG  
ACCCACGCGTCCGCGGACGCGTGGGCGGACGCGTGGGCCGGCTACCAGGAAGAGTCTGCC  
GAAGGTGAAGGCCATGGACTTCATCACCTCCACAGCCATCCTGCCCCCTGCTGTTCCGGCTG  
CCTGGGCGTCTTCGGCCTCTTCCGGCTGCTGCAGTGGGTGCGCGGGAAGGCCTACCTGCG  
GAATGCTGTGGTGGTGATCACAGGCGCCACCTCAGGGCTGGGCAAAGAATGTGCAAAAGT  
CTTCTATGCTGCGGGTGCTAAACTGGTGCTCTGTGGCCGGAATGGTGGGGCCCTAGAAGA  
GCTCATCAGAGAACTTACCGCTTCTCATGCCACCAAGGTGCAGACACACAAGCCTTACTT  
GGTGACCTTCGACCTCACAGACTCTGGGGCCATAGTTGCAGCAGCAGCTGAGATCCTGCA  
GTGCTTTGGCTATGTGACATACTTGTCACAATGCTGGGATCAGCTACCGTGGTACCAT  
CATGGACACCACAGTGGATGTGGACAAGAGGGTTCATGGAGACAACTACTTTGGCCCAGT  
TGCTCTAACGAAAGCACTCCTGCCCCCCTCATGATCAAGAGGAGGCAAGGCCACATTGTGCGC  
CATCAGCAGCATCCAGGGCAAGATGAGCATTCCCTTTTCGATCAGCATATGCAGCCTCCAA  
GCACGCAACCCAGGCTTTCTTTGACTGTCTGCGTGCCGAGATGGAACAGTATGAAATTGA  
GGTGACCGTCATCAGCCCCGGCTACATCCACACCAACCTCTCTGTAAATGCCATCACCGC  
GGATGGATCTAGGTATGGAGTTATGGACACCACCACAGCCCAGGGCCGAAGCCCTGTGGA  
GGTGGCCCAGGATGTTCTTGCTGCTGTGGGGAAGAAGAAGAAAGATGTGATCCTGGCTGA  
CTTACTGCCTTCCTTGGCTGTTTATCTTCGAACTCTGGCTCCTGGGCTCTTCTTCAGCCT  
CATGGCCTCCAGGGCCAGAAAAGAGCGGAAATCCAAGAACTCCTAGTACTCTGACCAGCC  
AGGGCCAGGGCAGAGAAGCAGCACTCTTAGGCTTGCTTACTCTACAAGGGACAGTTGCAT  
TTGTTGAGACTTTAATGGAGATTTGTCTCACAAGTGGGAAAGACTGAAGAAACACATCTC  
GTGCAGATCTGCTGGCAGAGGACAATCAAAAACGACAACAAGCTTCTTCCCAGGGTGAGG  
GGAAACACTTAAGGAATAAATATGGAGCTGGGGTTTAACACTAAAACTAGAAATAAACA  
TCTCAAACAGTAAAAAAAAAAAAAAAAAGGGCGGCCGCGACTCTAGAGTCGACCTGCAGAAG  
CTTGGCCGCCATGGCCCAACTTGTTTATTGCAGCTTATAATGGTTAC

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**FIGURE 38**

MDFITSTAILPLLFGCLGVFGLFRLLQWVRGKAYLRNAVVVITGATSGLGKECAKVFYAA  
GAKLVLCGRNGGALEELIRELTASHATKVQTHKPYLVTFDLTDSGAIVAAAAEILQCFGY  
VDILVNNAGISYRGTIMDTTVDDVKRVMETNYFGPVALTKALLPSMIKRRQGHIVAIS  
QGKMSIPFRSAYAASKHATQAFFDCLRAEMEQYEIEVTVISPGYIHTNLSVNAITADGSR  
YGVMDTTTAQGRSPVEVAQDVLAAVGKKKKDVLADLLPSLAVYLRTLAPGLFFSLMASR  
ARKERKSKNS

**Signal sequence:**

amino acids 1-21

**Transmembrane domain:**

amino acids 104-120, 278-292

**N-glycosylation site:**

amino acids 228-232

**Glycosaminoglycan attachment site:**

amino acids 47-51

**Casein kinase II phosphorylation site:**

amino acids 135-139, 139-143, 253-257

**Tyrosine kinase phosphorylation site:**

amino acids 145-153, 146-153

**N-myristoylation site:**

amino acids 44-50, 105-111, 238-244, 242-248, 291-297

**Amidation site:**

amino acids 265-269

**Prokaryotic membrane lipoprotein lipid attachment site:**

amino acids 6-17

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## FIGURE 39

GCAAGCCAAGGCGCTGTTTGAAGAAGTTCGGACCCATGTGGAGGAGGGGGACATTGT  
GTACCGCCTCTACATGCGGCAGACCATCATCAAGGTGATCAAGTTCATCCTCATCATCTGCTACAC  
CGTCTACTACGTGCACAACATCAAGTTTCGACGTGGACTGCACCGTGGACATTGAGAGCCTGACGGG  
CTACCGCACCTACCGCTGTGCCCCACCCCTGGCCACACTCTTCAAGATCCTGGCGTCTTTCTACAT  
CAGCCTAGTCATCTTTACGGCCTCATCTGCATGTACACACTGTGGTGGATGCTACGGCGCTCCCT  
CAAGAAGTACTCGTTTGAAGTCGATCCGTGAGGAGAGCAGCTACAGCGACATCCCCGACGTCAAGAA  
CGACTTCGCCTTCATGCTGCACCTCATTGACCAATACGACCCGCTCTACTCCAAGCGCTTCGCCGT  
CTTCCTGTGCGAGGTGAGTGAGAACAAAGCTGCGGCAGCTGAACCTCAACAACGAGTGGACGCTGGA  
CAAGCTCCGGCAGCGGCTCACCAGAAGCGCGCAGGACAAGCTGGAGCTGCACCTGTTTCATGCTCAG  
TGGCATCCCTGACACTGTGTTTGACCTGGTGGAGCTGGAGGTCTCAAGCTGGAGCTGATCCCCGA  
CGTGACCATCCCGCCCAGCATTGCCCAGCTCACGGGCCTCAAGGAGCTGTGGCTCTACCACACAGC  
GGCCAAGATTGAAGCGCCTGCGCTGGCCTTCCTGCGCGAGAACCTGCGGGCGCTGCACATCAAGTT  
CACCGACATCAAGGAGATCCCGCTGTGGATCTATAGCCTGAAGACACTGGAGGAGCTGCACCTGAC  
GGGCAACCTGAGCGCGGAGAACAAACCGCTACATCGTCATCGACGGGCTGCGGGAGCTCAAACGCCT  
CAAGGTGCTGCGGCTCAAGAGCAACCTAAGCAAGCTGCCACAGGTGGTCAAGATGTGGGCGTGCA  
CCTGCAGAAGCTGTCCATCAACAATGAGGGCACCAGCTCATCGTCCTCAACAGCCTCAAGAAGAT  
GGCGAACCTGACTGAGCTGGAGCTGATCCGCTGCGACCTGGAGCGCATCCCCACTCCATCTTCAG  
CCTCCACAACCTGCAGGAGATTGACCTCAAGGACAACAACCTCAAGACCATCGAGGAGATCATCAG  
CTTCAGCACCTGCACCGCCTCACCTGCCTTAAGCTGTGGTACAACCACATCGCCTACATCCCCAT  
CCAGATCGGCAACCTCACCAACCTGGAGCGCCTCTACCTGAACCGCAACAAGATCGAGAAGATCCC  
CACCCAGCTCTTCTACTGCCGCAAGCTGCGCTACCTGGACCTCAGCCACAACAACCTGACCTTCCT  
CCCTGCCGACATCGGCCTCCTGCAGAACCTCCAGAACCTAGCCATCACGGCCAACCGGATCGAGAC  
GCTCCCTCCGGAGCTCTTCCAGTGCCGGAAGCTGCGGGCCCTGCACCTGGGCAACAACGTGCTGCA  
GTCACTGCCCTCCAGGGTGGGCGAGCTGACCAACCTGACGCAGATCGAGCTGCGGGGCAACCGGCT  
GGAGTGCCCTGCCTGTGGAGCTGGGCGAGTGCCCACTGCTCAAGCGCAGCGGCTTGGTGGTGGAGGA  
GGACCTGTTCAACACACTGCCACCCGAGGTGAAGGAGCGGCTGTGGAGGGCTGACAAGGAGCAGGC  
CTGAGCGAGGCCGGCCCAGCACAGCAAGCAGCAGGACCGCTGCCAGTCTCAGGCCCGGAGGGGC  
AGGCCTAGCTTCTCCAGAACTCCCGGACAGCCAGGACAGCCTCGCGGCTGGGCAGGAGCCTGGGG  
CCGCTTGTGAGTCAGGCCAGAGCGAGAGGACAGTATCTGTGGGGCTGGCCCTTTTCTCCCTCTGA  
GACTCAGTCCCCCAGGGCAAGTGCTTGTGGAGGAGCAAGTCTCAAGAGCGCAGTATTTGGATA  
ATCAGGGTCTCCTCCCTGGAGGCCAGCTCTGCCCCAGGGCTGAGCTGCCACCAGAGTCTTGGGA  
CCCTCACTTTAGTTCTTGGTATTTATTTTCTCCATCTCCACCTCCTTCATCCAGAGTAATATA  
CATTCCCAAGAAAGTTTCAGCCCAGATGGAAGGTGTTTCAGGAAAGGTGGGCTGCCTTTTCCCTTTG  
TCCTTATTTAGCGATGCCGCGGGCATTTAACACCCACCTGGACTTCAGCAGAGTGGTCCGGGGCG  
AACCAGCCATGGGACGGTCACCCAGCAGTGCCGGGCTGGGCTCTGCGGTGCGGTCCACGGGAGAGC  
AGGCCTCCAGCTGGAAGGCCAGGCCTGGAGCTTGCCCTTTCAGTTTTTGTGGCAGTTTTAGTTTT  
TTGTTTTTTTTTTTTTTAATCAAAAAACAATTTTTTTTAAAAAAAAGCTTTGAAAATGGATGGTTT  
GGGTATTAAAAAGAAAAAAAACCTTAAAAAAAAGACACTAACGGCCAGTGAGTTGGAGTCTC  
AGGGCAGGGTGGCAGTTTCCCTTGAGCAAAGCAGCCAGACGTTGAACCTGTGTTTTCTTTCCCTGGG  
CGCAGGGTGCAGGGTGTCTTCCGGATCTGGTGTGACCTTGGTCCAGGAGTTCTATTTGTTCCCTGGG  
GAGGGAGGTTTTTTTTGTTTGTGTTTTTGGGTTTTTTTTGGTGTCTTGTGTTTTCTTCTCCTCCATGTGT  
CTTGGCAGGCACTCATTTCTGTGGCTGTCCGGCCAGAGGGAATGTTCTGGAGCTGCCAAGGAGGGAG  
GAGACTCGGGTTGGCTAATCCCCGGATGAACGGTGTCTCCATTCGCACCTCCCCCTCCTCGTGCTGC  
CCTGCCTCTCCACGCACAGTGTTAAGGAGCCAAGAGGAGCCACTTCGCCCAGACTTGTGTTTCCCCA  
CCTCCTGCGGCTGAGTGGGTGTGTCAGTGCCACCGCTGGCCTCCGCTGCTTCCATCAGCCCTGTGC  
ACCTGGTCTCTTCATGAAGAGCAGACACTTAGAGGCTGGTGGGAATGGGGAGGTGCCCCCTGGGAG  
GGCAGGCGTTGGTTCCAAGCCGTTCCCGTCCCTGGCGCTGGAGTGACACAGCCCGAGTGGGCAC  
CTGGTGGCTGGAAGCCAACCTGCTTTAGATCACTCGGGTCCCCACCTTAGAAGGGTCCCCGCTTA  
GATCAATCACGTGGACACTAAGGCACGTTTTAGAGTCTCTTGTCTTAATGATTATGTCCATCCGTC  
TGTCGGTCCATTTGTGTTTTCTGCGTGTGTGATTGGATATAATCCTCAGAAATAATGCACACTAG  
CCTCTGACAACCATGAAGCAAAAATCCGTTACATGTGGGTCTGAACCTGTAGACTCGGTACAGTA  
TCAAATAAATCTATAACAGAAAAA

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**FIGURE 40**

MRQTIKVIKFILIIICYTVYYVHNIKFDVDCTVDIESLTGYRITYRCAHPLATLFKILASF  
YISLVIFYGLICMYTLWWMRLRRSLKKYSFESIREESSYSDIPDVKNDFAFMLHLIDQYDP  
LYSKRFAVFLSEVSENKLRQLNLNNEWTLDKLRQRLTKNAQDKLELHFLMLSGIPDTVFD  
LVELEVLKLELIPDVTIPPSIAQLTGLKELWLYHTAAKIEAPALAFLENLRALHIKFTD  
IKEIPLWIYSLKTLEELHLTGNLSAENNRYIVIDGLRELKRLKVLRLKSNLSKLPQVVD  
VGVHLQKLSINNEGTKLIVLNSLKKMANLTELELIRCDLERIPHSIFSLHNLQEIDLKDN  
NLKTIIEIISFQHLHRLTCLKLWYNHIAIYIPIQIGNLTNLERLYLNRNKIEKIPTQLFYC  
RKLRYLDLSHNNLTFLPADIGLLQNLQNLAITANRIETLPPELFQCRKLRLHLGNNVLQ  
SLPSRVGELTNLTQIELRGNRLECLPVELGECPLLKRSGLVVEEDLFNTLPPEVKERLWR  
ADKEQA

**Transmembrane domain:**  
amino acids 51-75 (type II)

**N-glycosylation site:**  
amino acids 262-266, 290-294, 328-332, 396-400, 432-436,  
491-495

**cAMP- and cGMP-dependent protein kinase phosphorylation site:**  
amino acids 85-89

**Casein kinase II phosphorylation site:**  
amino acids 91-95, 97-101, 177-181, 253-257, 330-334, 364-368,  
398-402, 493-497

**N-myristoylation site:**  
amino acids 173-179, 261-267, 395-401, 441-447

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## FIGURE 41

GGGGGAGAAGGCGGCCGAGCCCCAGCTCTCCGAGCACCGGGTCGGAAGCCGCGACCCGAG  
CCGCGCAGGAAGCTGGGACCGGAACCTCGGCGGACCCGGCCCCACCCAACTCACCTGCGC  
AGGTCACCAGCACCCCTCGGAACCCAGAGGCCCGCGCTCTGAAGGTGACCCCCCTGGGGAG  
GAAGGCGATGGCCCCCTGCGAGGACGATGGCCCGCGCCCGCTCGCCCCGGCCGGCATCCC  
TGCCGTGCGCTTGTGGCTTCTGTGCACGCTCGGCCTCCAGGGCACCCAGGCCGGGCCACC  
GCCCCGCCCCCTGGGCTGCCCCGCGGGAGCCGACTGCCTGAACAGCTTTACCGCCGGGGT  
GCCTGGCTTCGTGCTGGACACCAACGCCTCGGTGAGCAACGGAGCTACCTTCCTGGAGTC  
CCCCACCGTGCGCCGGGGCTGGGACTGCGTGCGCGCCTGCTGCACCACCCAGAACTGCAA  
CTTGCGCTAGTGGAGCTGCAGCCCGACCGCGGGGAGGACGCCATCGCCGCTGCTTCCT  
CATCAACTGCCTCTACGAGCAGAACTTCGTGTGCAAGTTTCGCGCCCAGGGAGGGCTTCAT  
CAACTACCTCACGAGGGAAGTGTACCGCTCCTACCGCCAGCTGCGGACCCAGGGCTTTGG  
AGGGTCTGGGATCCCCAAGGCCTGGGCAGGCATAGACTTGAAGGTACAACCCAGGAACC  
CCTGGTGCTGAAGGATGTGGAAAACACAGATTGGCGCCTACTGCGGGGTGACACGGATGT  
CAGGGTAGAGAGGAAAGACCCAAACCAGGTGGAAGTGTGGGGACTCAAGGAAGGCACCTA  
CCTGTTCCAGCTGACAGTGACTAGCTCAGACCACCCAGAGGACACGGCCAAACGTACAGT  
CACTGTGCTGTCCACCAAGCAGACAGAAGACTACTGCCTCGCATCCAACAAGGTGGGTCTG  
CTGCCGGGGCTCTTTCCACGCTGGTACTATGACCCACGGAGCAGATCTGCAAGAGTTT  
CGTTTATGGAGGCTGCTTGGGCAACAAGAACAACCTACCTTCGGGAAGAAGAGTGCATTCT  
AGCCTGTGCGGGGTGTGCAAGGTGGGCCTTTGAGAGGCAGCTCTGGGGCTCAGGCGACTTT  
CCCCCAGGGCCCCCTCCATGGAAAGGCGCCATCCAGTGTGCTCTGGCACCTGTCAGCCAC  
CCAGTTCGCGTGACGAATGGCTGCTGCATCGACAGTTTCCTGGAGTGTGACGACACCCC  
CAACTGCCCCGACGCCTCCGACGAGGCTGCCTGTGAAAAATACACGAGTGGCTTTGACGA  
GCTCCAGCGCATCCATTTCCCCAGTGACAAAGGGCACTGCGTGGACCTGCCAGACACAGG  
ACTCTGCAAGGAGAGCATCCCGCGCTGGTACTACAACCCCTTCAGCGAACACTGCGCCCCG  
CTTTACCTATGGTGGTTGTTATGGCAACAAGAACAACCTTTGAGGAAGAGCAGCAGTGCCT  
CGAGTCTTGTGCGGCATCTCCAAGAAGGATGTGTTTGGCCTGAGGCGGGAAATCCCCAT  
TCCAGCACAGGCTCTGTGGAGATGGCTGTACAGTGTTCCTGGTCATCTGCATTGTGGT  
GGTGGTAGCCATCTTGGGTACTGCTTCTTCAAGAACCCAGAGAAAGGACTTCCACGGACA  
CCACCACACCCACCCACCCCTGCCAGCTCCACTGTCTCCACTACCGAGGACACGGA  
GCACCTGGTCTATAACCACACCCCGGCCCTCTGAGCCTGGGTCTCACCGGCTCTCAC  
CTGGCCCTGCTTCTGCTTGCCTGCTTGCCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCT  
ACTCTTGCCTGTTTCCCAGGCCCCACTGTGCTCAGAGACCAGGGCTCCAGCCCCCTCTTG  
AGAAGTCTCAGCTAAGCTCACGTCTGAGAAAGCTCAAAGGTTTGAAGGAGCAGAAAAAC  
CCTTGGGCCCAGAAGTACCAGACTAGATGGACCTGCCTGCATAGGAGTTTGGAGGAAGTTG  
GAGTTTTGTTTCTCTGTTCAAAGCTGCCTGTCCCTACCCCATGGTGCTAGGAAGAGGAG  
TGGGGTGGTGTGACACCCTGGAGGCCCAACCTGTCTCCCGAGCTCCTCTTCCATGCT  
GTGCGCCCAGGGCTGGGAGGAAGGACTTCCCTGTGTAGTTTGTGCTGTAAAGAGTTGCTT  
TTTGTATTATTAATGCTGTGGCATGGGTGAAGAGGAGGGGAAGAGGCCTGTTTGGCCTCT  
CTGTCTCTCTTCTCTTCCCCAAGATTGAGCTCTCTGCCCTTGATCAGCCCCACCCCTG  
GCCTAGACCAGCAGACAGAGCCAGGAGAGGCTCAGCTGCATTCCGCGAGCCCCACCCCA  
AGGTTCTCCAACATCACAGCCCAGCCCACCCACTGGGTAATAAAAGTGGTTTGTGGAAAA  
AAAAAAAAAAAAAAAAAAAAA

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**FIGURE 42**

MAPARTMARARLAPAGIPAVALWLLCTLGLQGTQAGPPPAPPGLPAGADCLNSFTAGVPG  
FVLDTNASVSNGATFLESPTVRRGWDCVRACCTTQNCNLALVELQPDRGEDAIAACFLIN  
CLYEQNFVCKFAPREGFINYLTVREYRSYRQLRTQGFGGSGIPKAWAGIDLKVQPQEPLV  
LKDVENTDWRLLRGDTDVRVERKDPNQVELWGLKEGTYLFQLTVTSSDHPEDTANVTVTV  
LSTKQTEDYCLASNKVGRCRGSFPRWYYDPTEQICKSFVYGGCLGNKNNYLREEECILAC  
RGVQGGPLRGSSGAQATFPQGSPMERRHPVCSGTCQPTQFRCSNGCCIDSFLECDTPNC  
PDASDEAAACEKYTSGFDELQRIHFPSDKGHCVDLPDTGLCKESIPRWYYPFSEHCARFT  
YGGCYGNKNNFEEEQQCLESRCRGISKKDVFGLRREIPIPTGSGVEMAVTVFLVICIVVV  
AILGYCFFKNQRKDFHGHHPPTPASSTVSTTEDTEHLVYNHTTRPL

**signal sequence:**

Amino acids 1-35

**transmembrane domain:**

Amino acids 466-483

**N-glycosylation sites:**

Amino acids 66-70;235-239;523-527

**N-myristoylation sites:**

A     m     i     n     o                     a     c     i     d     s  
29-35;43-49;161-167;212-218;281-287;282-288;285-291;  
310-316;313-319;422-428;423-429;426-432

**Cell attachment sequence:**

Amino acids 193-199

**Pancreatic trypsin inhibitor (Kunitz) family signatures:**

Amino acids 278-298;419-438

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**FIGURE 43**

CCCACGCGTCCGCACCTCGGCCCCGGGCTCCGAAGCGGCTCGGGGGCGCCCTTTTCGGTCA  
ACATCGTAGTCCACCCCCTCCCCATCCCCAGCCCCCGGGATTTCAGGCTCGCCAGCGCCC  
AGCCAGGGAGCCGGCCGGAAGCGCGATGGGGGGCCCCAGCCGCCTCGCTCCTGCTCCTGC  
TCCTGCTGTTTCGCCTGCTGCTGGGCGCCCGGGGGCCAACTCTCCCAGGACGACAGCC  
AGCCCTGGACATCTGATGAAACAGTGGTGGCTGGTGGCACCGTGGTGCTCAAGTGCCAAG  
TGAAAGATCACGAGGACTCATCCCTGCAATGGTCTAACCCTGCTCAGCAGACTCTCTACT  
TTGGGGAGAAGAGAGCCCTTCGAGATAATCGAATTCAGCTGGTTACCTCTACGCCCCACG  
AGCTCAGCATCAGCATCAGCAATGTGGCCCTGGCAGACGAGGGCGAGTACACCTGCTCAA  
TCTTCACTATGCCTGTGCGAACTGCCAAGTCCCTCGTCACTGTGCTAGGAATTCACAGA  
AGCCCATCATCACTGGTTATAAATCTTCATTACGGGAAAAAGACACAGCCACCCTAACT  
GTCAGTCTTCTGGGAGCAAGCCTGCAGCCCGGCTCACCTGGAGAAAGGGTGACCAAGAAC  
TCCACGGAGAACCAACCCGCATACAGGAAGATCCCAATGGTAAACCTTCACTGTCAGCA  
GCTCGGTGACATTCCAGGTTACCCGGGAGGATGATGGGGCGAGCATCGTGCTCTGTGA  
ACCATGAATCTCTAAAGGGAGCTGACAGATCCACCTCTCAACGCATTGAAGTTTATACA  
CACCAACTGCGATGATTAGGCCAGACCCTCCCCATCCTCGTGAGGGCCAGAAGCTGTTGC  
TACACTGTGAGGGTCGCGGCAATCCAGTCCCCCAGCAGTACCTATGGGAGAAGGAGGGCA  
GTGTGCCACCCCTGAAGATGACCCAGGAGAGTGCCCTGATCTTCCCTTTCTCAACAAGA  
GTGACAGTGGCACCTACGGCTGCACAGCCACCAGCAACATGGGCAGCTACAAGGCCTACT  
ACACCCTCAATGTTAATGACCCAGTCCGGTGCCCTCCTCCTCCAGCACCTACCACGCCA  
TCATCGGTGGGATCGTGGCTTTTATTGTCTTCTGCTGCTCATCATGCTCATCTTCTTG  
GCCACTACTTGATCCGGCACAAAGGAACCTACCTGACACATGAGGCAAAAGGCTCCGACG  
ATGCTCCAGACGCGGACACGGCCATCATCAATGCAGAAGGCGGGCAGTCAGGAGGGGACG  
ACAAGAAGGAATATTTTCATCTAGAGGGCGCTGCCCACTTCTGCGCCCCCAGGGGCCCT  
GTGGGGACTGCTGGGGCCGTACCAACCCGGACTTGTACAGAGCAACCGCAGGGCCGCC  
CTCCCGCTTGCTCCCCAGCCACCCACCCCTGTACAGAATGTCTGCTTTGGGTGCGGT  
TTTGTACTCGGTTTGAATGGGGAGGGAGGAGGGCGGGGGAGGGGAGGGTTGCCCTCAG  
CCCTTTCGCTGGCTTCTCTGCATTTGGGTATTATTATTTTGTAAACATCCCAAATCAA  
ATCTGTCTCCAGGCTGGAGAGGCAGGAGCCCTGGGGTGAGAAAAGCAAAAACAAACAA  
AAACA

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**FIGURE 44**

MGAPAASLLLLLLFACCWAPGGANLSQDDSQPWTSDETVVAGGTVVLKCQVKDHEDSSL  
QWSNPAQQTLYFGEKRALRDNRIQLVTSTPHELSSISINVALADEGEYTCSTFTMPVRTA  
KSLVTVLGIPQKPIITGYKSSLREKDTATLNCQSSGSKPAARLTWRKGDQELHGEPTRIQ  
EDPNGKTFTVSSSVTFQVTRDDGASIVCSVNHESLKGADRSTSQRIEVLYTPTAMIRPD  
PPHPREGQKLLHCEGRGNPVPQQYLWEKEGSVPPLKMTQESALIFPFLNKSDSGTYGCT  
ATSNMGSYKAYYTLNVNDPSPVPSSSSTYHAIIGGIVAFIVFLLIMLIFLGHYLIRHKG  
TYLTHEAKGSDDAPDADTAIINAEGGQSGGDDKKEYFI

**Signal sequence:**

amino acids 1-20

**Transmembrane domain:**

amino acids 331-352

**N-glycosylation site:**

amino acids 25-29, 290-294

**Casein kinase II phosphorylation site:**

amino acids 27-31, 35-39, 89-93, 141-145, 199-203, 388-392

**N-myristoylation site:**amino acids 2-8, 23-29, 156-162, 218-224, 295-301, 298-304,  
306-310, 334-340, 360-364, 385-389, 386-390**Prokaryotic membrane lipoprotein lipid attachment site:**

amino acids 7-18



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**FIGURE 45**

ACTTGCCATCACCTGTTGCCAGTGTGGAAAAATTCTCCCTGTTGAATTTTTTGCACATGG  
AGGACAGCAGCAAAGAGGGCAACACAGGCTGATAAGACCAGAGACAGCAGGGAGATTATT  
TTACCATACGCCCTCAGGACGTTCCCTCTAGCTGGAGTTCTGGACTTCAACAGAACCCCA  
TCCAGTCATTTTGATTTTGCTGTTTATTTTTTTTTTCTTTTTCTTTTTCCCACCACATTG  
TATTTTATTTCCGTACTTCAGAAATGGGCCTACAGACCACAAAGTGGCCCAGCCATGGGG  
CTTTTTTCTGAAGTCTTGGCTTATCATTCCCTGGGGCTCTACTCACAGGTGTCCAAAC  
TCCTGGCCTGCCCTAGTGTGTGCCGCTGCGACAGGAACTTTGTCTACTGTAATGAGCGAA  
GCTTGACCTCAGTGCCTCTTGGGATCCCGGAGGGCGTAACCGTACTCTACCTCCACAACA  
ACCAAATTAATAATGCTGGATTTCCCTGCAGAACTGCACAATGTACAGTCGGTGCACACGG  
TCTACCTGTATGGCAACCAACTGGACGAATTCCCCATGAACCTTCCCAAGAATGTAGAG  
TTCTCCATTTGCAGGAAAACAATATTCAGACCATTTACGGGCTGCTCTTGCCCAGCTCT  
TGAAGCTTGAAGAGCTGCACCTGGATGACAACCTCCATATCCACAGTGGGGGTGGAAGACG  
GGGCCTTCCGGGAGGCTATTAGCCTCAAATTGTTGTTTTGTCTAAGAATCACCTGAGCA  
GTGTGCCTGTTGGGCTTCCCTGTGGACTTGCAAGAGCTGAGAGTGGATGAAAATCGAATTG  
CTGTCATATCCGACATGGCCTTCCAGAATCTCACGAGCTTGGAGCGTCTTATTGTGGACG  
GGAACCTCCTGACCAACAAGGTATCGCCGAGGGCACCTTCAGCCATCTCACCAAGCTCA  
AGGAATTTTCAATTGTACGTAATTGCTGTCCCACCCTCCTCCCGATCTCCCAGGTACGC  
ATCTGATCAGGCTCTATTGTCAGGACAACCAGATAAACCACATTCCTTTGACAGCCTTCT  
CAAATCTGCGTAAGCTGGAACGGCTGGATATATCCAACAACCAACTGCGGATGCTGACTC  
AAGGGGTTTTTGATAATCTCTCCAACCTGAAGCAGCTCACTGCTCGGAATAACCCTTGGT  
TTTGTGACTGCAGTATTAAATGGGTACAGAATGGCTCAAATATATCCCTTCATCTCTCA  
ACGTGCGGGGTTTCATGTGCCAAGGTCTGAACAAGTCCGGGGGATGGCCGTCAGGGAAT  
TAAATATGAATCTTTTGTCTGTCCCACCACGACCCCCGGCCTGCCTCTCTTACCCCGAG  
CCCCAAGTACAGCTTCTCCGACCACTCAGCCTCCCACCCTCTCTATTCCAAACCCTAGCA  
GAAGCTACACGCCTCCAACCTCTACCACATCGAAACTTCCCACGATTCCTGACTGGGATG  
GCAGAGAAAGAGTGACCCACCTATTTCTGAACGGATCCAGCTCTCTATCCATTTTGTGA  
ATGATACTTCCATTCAAGTCAGCTGGCTCTCTCTCTTACCGTGATGGCATAAACTCA  
CATGGGTGAAAATGGGCCACAGTTTAGTAGGGGGCATCGTTCAGGAGCGCATAGTCAGCG  
GTGAGAAGCAACACCTGAGCCTGGTTAACTTAGAGCCCCGATCCACCTATCGGATTTGTT  
TAGTGCCACTGGATGCTTTTAACTACCGCGCGGTAGAAGACACCATTTGTTTCAGAGGCCA  
CCACCCATGCCTCCTATCTGAACAACGGCAGCAACACAGCGTCCAGCCATGAGCAGACGA  
CGTCCCACAGCATGGGCTCCCCCTTCTGCTGGCGGGCTTGATCGGGGGCGCGGTGATAT  
TTGTGCTGGTGGTCTTGCTCAGCGTCTTTTGCTGGCATATGCACAAAAGGGGCGCTACA  
CCTCCCAGAAGTGGAATAACAACGGGGCGGGCGGAAAGATGATTATTGCGAGGCAGGCA  
CCAAGAAGGACAACCTCCATCCTGGAGATGACAGAAACCAGTTTTTCAGATCGTCTCCTTAA  
ATAACGATCAACTCCTTAAAGGAGATTTAGACTGCAGCCCATTTACACCCCAAATGGGG  
GCATTAATTACACAGACTGCCATATCCCCAACACATGCGATACTGCAACAGCAGCGTGC  
CAGACCTGGAGCACTGCCATACGTCAGCCAGAGGCCAGCGTTATCAAGGCGGACAAT  
TAGACTCTTGAGAACACACTCGTGTGTGCACATAAAGACACGCAGATTACATTTGATAAA  
TGTTACACAGATGCATTTGTGCATTTGAATACTCTGTAATTTATACGGTGTACTATATAA  
TGGGATTTAAAAAAGTGCTATCTTTTCTATTTCAAGTTAATTACAAACAGTTTTGTAAAC  
TCTTTGCTTTTTTAAATCTT

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**FIGURE 46**

MGLQTTKWPSHGAFFLKSWLIISLGLYSQVSKLLACPSVCRCDRNFVYCNERSLTSVPLG  
IPEGVTVLVYLHNNQINNAGFPaelhNVQSVHTVYLYGNQLDEFFPMNLPKNVRVLHLQENN  
IQTISRALAQLLKLEELHDDNSISTVGVEDGAFREAI SLKLLFLSKNHLSSVPVGLPV  
DLQELRVDENRIAVISDMAFQNLTSLERLIVDGNLLTNKGIAEGTFSHLT KLKEFSIVRN  
SLSHPPPDLPGTHLIRLYLQDNQINHIPLTAFSNLRKLERLDISNNQLRMLTQGVFDNLS  
NLKQLTARNNPWFCDCSI KWVTEWLKYIPSSLNVRGFMCGPEQVRGMVRELNMNLLSC  
PTTTPGLPLFTPAPSTASPTTQPPTLSIPNPSRSYTPPTPTTSKLPTIPDWDGRERVTPP  
ISERIQLSIHFVNDSIQVSWLSLFTVMAYKLTWVKMGHSLVGGIVQERIVSGEKQHL SL  
VNLEPRSTYRICLVPLDAFN YRAVEDTICSEATTHASYLNNGSNTASSHEQTTSHSMGSP  
FLLAGLIGGAVIFVLVLLSVFCWHMHKKGRYTSQKWYNRGRRKDDYCEAGTKKDNSIL  
EMTETSFQIVSLNNDQLLKGD FRLQPIYTPNGGINYTDCHIPNNMRYCNSSVPDLEHCHT

**Signal peptide:**

amino acids 1-42

**Transmembrane domain:**

amino acids 542-561

**N-glycosylation site:**amino acids 202-206, 298-302, 433-437, 521-525, 635-639,  
649-653**Casein kinase II phosphorylation site:**amino acids 204-208, 407-411, 527-531, 593-597, 598-602,  
651-655**Tyrosine kinase phosphorylation site:**

amino acids 319-328

**N-myristoylation site:**amino acids 2-8, 60-66, 149-155, 213-219, 220-226, 294-300,  
522-528, 545-551, 633-639**Amidation site:**

amino acids 581-585

**Leucine zipper pattern:**

amino acids 164-186

**Phospholipase A2 aspartic acid active site:**

amino acids 39-50

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**FIGURE 47**

GCAGCGAGCGCCGGGTGCGGCCCTGCCGCCGAGGGATGTGACCTTCACCGTCGCTTAGC  
CAGGATGACCGGAGCCCGTGTCTCGCGGCGTCCGCGCCTCGCTTCAGCCTCCCGGGTGCT  
CTGACCGCACGCTCCCGGCTGCTAGGCTCCCGGCGACCGGCCCTCGCCATGCGGCCACCGC  
CCGGGCCCGCCGCCCGCCCTGGGCACTGCGCTTCTGCTGCTCCTGCTGGCTTCCGAGTCTT  
CTCACACTGTGCTGTTGCGGGCGCGTGAGGCGGCGCAGTTTCTGCGGCCAGGCAGCGCC  
GCGCCTACCAAGTCTTCGAGGAGGCCAAGCAGGGCCACCTGGAACGGGAGTGCCTGGAGG  
AGGTGTGCAGCAAAGAGGAGGCCAGAGAGGTGTTGAGAACGACCCCGAGACGGAGTATT  
TCTATCCACGATATCAAGAGTGCATGAGAAAATATGGCAGGCCTGAAGAAAAAAACCCAG  
ATTTTCGCCAAATGTGTTTCAAGACTTGCCCTGACCAGTGCACCCCAAACCTTGTGATAAGA  
AGGGTACTCATATCTGCCAAGACCTCATGGGCAACTTCTTCTGCGTGTGCACAGATGGCT  
GGGGAGGCGCGCTCTGTGACAAAGATGTCAATGAGTGTGTCCAGAAGAATGGGGGCTGCA  
GCCAGGTCTGCCACAACAAACCAGGAAGCTTCCAATGTGCCTGCCATAGTGGCTTCTCGC  
TTGCATCAGACCGGCCAGACCTGCCAAGATATCGATGAATGCACAGACTCAGACACCTGTG  
GGGACGCGCGATGCAAGAACTTGCCAGGCTCCTACTCTTGCCCTGCGATGAGGGATATA  
CATAAGCTCCAAGGAGAAGACCTGCCAAGATGTGGACGAGTGCCAGCAGGATCGCTGTG  
AGCAGACCTGTGTCAACTCCCAGGCAGCTATACCTGCCACTGTGATGGGCGAGGGGGCC  
TAAAACTATCCCAGACATGGATACTTGTGAGGACATCTTACCATGTGTGCCCTTCAGCA  
TGGCCAAGAGCGTGAAGTCTTGTACCTGGGCGCATGTTTACGCGGACCCCCGTGATTA  
GACTACGCTTCAAGAGGCTTCAGCCTACCAGGCTGCTGGCTGAATTTGACTTCCGCACCTT  
TTGACCCCTGAAGGAGTCTCTTCTTCTGCTGGAGGCCGTTTACAGACAGCACCTGGATTGTCC  
TGGGCCTAAGAGCTGGGCGGCTTGAGCTGCAGCTTTCGGTACAATGGCGTTGGGCGCATCA  
CCAGCAGCGGGCCAACCATCAACCACGGCATGTGGCAAACCTATCTCCGTGGAAGAGCTGG  
AACGTAACCTTGTGCATCAAGGTCAACAAAGATGCTGTAATGAAGATCGCGGTAGCTGGGG  
AGCTGTTTTCAGCTGGAGAGGGGCTCTATCACCTGAATCTCACCGTGGGCGGCATTCCCT  
TCAAGGAGAGTGAGCTCGTCCAGCCGATTAACCCCTCGCCTGGATGGGTGCATGAGGAGTT  
GGAAGTGGCTGAACGGGGAAGACAGCGCCATCCAGGAGACAGTCAAGGCAAACACAAAAA  
TGCAGTGCTTCTCTGTGACAGAAAGGGGCTCCTTCTTCCCGGGGAATGGATTGTGCTACCT  
ACAGGCTCAACTACACCCGAACATCGCTGGATGTGCGCACGGAAACACCTGGGAAGTTA  
AAGTTGTGGCTCGGATCCGCCCTGCCACGGACACGGGGGTGCTGCTGGCGCTGGTGGGGG  
ACGACGATGTGCTCATCTCTGTGGCCCTAGTCGACTACCACTCTACAAAGAAGCTCAAGA  
AGCAGTTGGTGGTCTTGGCAGTTGAGGATGTTGCCCTGGCACTGATGGAAATCAAGGTGT  
GCGACAGCCAGGAACACACGGTCACTGTCTCCCTGCGGGAGGGTGAGGCCACCTAGAAG  
TGGATGGCACAAAGGGCCAGAGTGAAGTGAGCACTGCCAGCTGCAGGAGCGACTGGACA  
CACTTAAGACACATCTGCAAGGCTCTGTGCACACCTATGTTGGAGGCCTGCCAGAAGTAT  
CGGTGATTTCTGCACCCGTCCTGCGTTCTACCGCGGATGCATGACTCTGGAGGTAAACG  
GGAAAATCCTGGACCTGGATACGGCCTCGTACAAGCACAGTGACATCACCTCCCACTCCT  
GCCCCGCTGTGGAGCATGCCACCCCTAGACCGAGCTGCAAGAGGGCTCCACACCTAAAG  
ACAAAAATGAAGCAGGGTTTGGACACACAGCACTGGCTCCTCTCGCATGGTCTTGCACA  
CTGGAGCAGCGTGGACCGCCCTTGTGGTTTTTTTTTTCTTGAGATCTTTCTTTTGCCTTG  
TAACATATCTGTACATAATGGACGGGTGTCGGGTACCGGCTGCTCAGAGAGAGCCACGT  
GACCTGGTGGGAGCTGGCTGGAAGGGGCTGGGCTAGAGGGGCTGGCAGTTTGCAGCAGAA  
CGGATGTGAAGAAAATAATTCTCTATTATTTTATTACTACATGCTTCTTCTGACTCTA  
AAATATGGAATAAATAATTTTACAGAAACCTTTTTTAAAAA

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**FIGURE 48**

MPPPPGPAAALGTALLLLLLLASESSHTVLLRAREAAQFLRPRQRRAYQVFEEAKQGHLE  
ECVEEVCSKEEAREVFENDPETEYFYPRYQECMRKYGRPEEKNPDAKCVQNLDPDQCTPN  
PCDKKGTHICQDLMGNFFCVCTDGWGGRLCDKDVNECVQKNGGCSQVCHNKPGSFQCACH  
SGFSLASDGQTCQDIDECTDSDTCGDARCKNLPGSYSCLCDEGYTYSSKEKTCQDVDECQ  
QDRCEQTCVNSPGSYTCHCDGRGGLKLSPDMDTCEDILPCVPFMSMAKS VKSLYLGRMFSG  
TPVIRLRFKRLQPTRLLAEFDFTFDPEGVLFFAGGRSDSTWIVLGLRAGRLELQLRYNG  
VGRITSSGPTINHGMWQTISVEELERNLVIKVNKDAVMKIAVAGELFQLERGLYHLNLT  
GGIPFKESELVQPINPRLDGCMRSWNWLNGEDSAIQETVKANTKMOCFSVTERGSFFPGN  
GFATYRLNYTRTSLDVGTETTWEVKVVARIRPATDTGVLLALVGDDDVVISVALVDYHST  
KKLKKQLVVLAVEDVALALMEIKVCDSEHTVTVSLREGEATLEVDTGKGQSEVSTAQLQ  
ERLDTLKTHLQGSVHTYVGGLPEVSVISAPVTA FYRGCMTLEVNGKILDLDTASYKHSDI  
TSHSCPPVEHATP

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**FIGURE 49**

CGCCGCGCTCCCGCACCCGCGGCCCGCCACCGCGCCGCTCCCGCATCTGCACCCGCAGC  
CCGGCGGCCTCCCGGCGGGAGCGAGCAGATCCAGTCCGGCCCCGAGCGCAACTCGGTCCA  
GTCGGGGCGGCGGCTGCGGGCGCAGAGCGGAGATGCAGCGGCTTGGGGCCACCCTGCTGT  
GCCTGCTGCTGGCGGGCGGCGGTCCCCACGGCCCCCGCGCCGCTCCGACGGCGACCTCGG  
CTCCAGTCAAGCCCGGCCCGGCTCTCAGTACCCGCAGGAGGAGGCCACCCTCAATGAGA  
TGTTCGCGGAGGTTGAGGAACTGATGGAGGACACGCAGCACAAATTGCGCAGCGCGGTGG  
AAGAGATGGAGGCAGAAGAAGCTGCTGCTAAAGCATCATCAGAAGTGAACCTGGCAAACCT  
TACCTCCCAGCTATCACAATGAGACCAACACAGACACGAAGGTTGGAAATAATACCATCC  
ATGTGCACCGAGAAATTACAAGATAACCAACAACCAGACTGGACAAATGGTCTTTTCAG  
AGACAGTTATCACATCTGTGGGAGACGAAGAAGGCAGAAGGAGCCACGAGTGCATCATCG  
ACGAGGACTGTGGGCCCAGCATGTACTGCCAGTTTGCCAGCTTCCAGTACACCTGCCAGC  
CATGCCGGGGCCAGAGGATGCTCTGCACCCGGGACAGTGAGTGCTGTGGAGACCAGCTGT  
GTGTCTGGGGTCACTGCACCAAAATGGCCACCAGGGGCAGCAATGGGACCATCTGTGACA  
ACCAGAGGGACTGCCAGCCGGGGCTGTGCTGTGCCCTTCCAGAGAGGCCTGCTGTTCCCTG  
TGTGCACACCCCTGCCCGTGGAGGGCGAGCTTTGCCATGACCCCGCCAGCCGGCTTCTGG  
ACCTCATCACCTGGGAGCTAGAGCCTGATGGAGCCTTGGACCGATGCCCTTGTGCCAGTG  
GCCTCCTCTGCCAGCCCCACAGCCACAGCCTGGTGTATGTGTGCAAGCCGACCTTCGTGG  
GGAGCCGTGACCAAGATGGGGAGATCCTGCTGCCAGAGAGGTCCCGATGAGTATGAAG  
TTGGCAGCTTCATGGAGGAGGTGCGCCAGGAGCTGGAGGACCTGGAGAGGAGCCTGACTG  
AAGAGATGGCGCTGGGGGAGCCTGCGGCTGCCGCCGCTGCACTGCTGGGAGGGGAAGAGA  
TTTAGATCTGGACCAGGCTGTGGGTAGATGTGCAATAGAAATAGCTAATTTATTTCCCCA  
GGTGTGTGCTTTAGGCGTGGGCTGACCAGGCTTCTTCCCTACATCTTCTTCCCAGTAAGTT  
TCCCCCTCTGGCTTGACAGCATGAGGTGTTGTGCATTTGTTTCAGCTCCCCCAGGCTGTTCT  
CCAGGCTTCACAGTCTGGTGCTTGGGAGAGTCAGGCAGGGTTAAACTGCAGGAGCAGTTT  
GCCACCCCTGTCCAGATTATTGGCTGCTTTGCCCTCTACCAGTTGGCAGACAGCCGTTTGT  
TCTACATGGCTTTGATAATTGTTTTGAGGGGAGGAGATGGAAACAATGTGGAGTCTCCCTC  
TGATTGGTTTTGGGGAAATGTGGAGAAGAGTGCCCTGCTTTGCAAAACATCAACCTGGCAA  
AAATGCAACAAATGAATTTTCCACGCAGTTCTTTCCATGGGCATAGGTAAGCTGTGCCTT  
CAGCTGTTGCAGATGAAATGTTCTGTTCCACCTGCATTACATGTGTTTATTTCATCCAGCA  
GTGTTGCTCAGCTCCTACCTCTGTGCCAGGGCAGCATTTTTCATATCCAAGATCAATTCCC  
TCTCTCAGCACAGCCTGGGGAGGGGGTCATTGTTCTCCTCGTCCATCAGGGATCTCAGAG  
GCTCAGAGACTGCAAGCTGCTTGCCCCAAGTCACACAGCTAGTGAAGACCAGAGCAGTTTC  
ATCTGGTTGTGACTCTAAGCTCAGTGCTCTCTCCACTACCCACACCAGCCTTGGTGCCA  
CCAAAAGTGCTCCCCAAAAGGAAGGAGAATGGGATTTTTCTTGAGGCATGCACATCTGGA  
ATTAAGGTCAAACCTAATTCTCACATCCCTCTAAAAGTAAACTACTGTTAGGAACAGCAGT  
GTTCTCACAGTGTGGGGCAGCCGTCTTCTAATGAAGACAATGATATTGACACTGTCCCT  
CTTTGGCAGTTGCATTAGTAACTTTGAAAGGTATATGACTGAGCGTAGCATACAGGTTAA  
CCTGCAGAAACAGTACTTAGGTAATTGTAGGGCGAGGATTATAAATGAAATTTGCAAAAT  
CACTTAGCAGCAACTGAAGACAATTATCAACCACGTGGAGAAAATCAAACCGAGCAGGGC  
TGTGTGAAACATGGTTGTAATATGCGACTGCGAACACTGAACTCTACGCCACTCCACAAA  
TGATGTTTTAGGTGTGATGGACTGTTGCCACCATGTATTTCATCCAGAGTTCTTAAAGTT  
TAAAGTTGCACATGATTGTATAAGCATGCTTTCTTTGAGTTTTAAATTATGTATAAACAT  
AAGTTGCATTTAGAAATCAAGCATAAATCACTTCAACTGCAAAAAAAAAAAAAAAAAAAAA  
AAAAAA

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**FIGURE 50**

MQRLGATLLCLLLAAAVPTAPAPAPTATSAPVKPGPALSYPQEEATLNEMFREVEELMED  
TQHKLRSAVEEMEAEAAAKASSEVNLANLPSPYHNETNTDTKVGNNNTIHVHREIHKITN  
NQTGQMVFSETVITSVGDEEGRRSHECIIDEDCGPSMYCQFASFQYTCQPCRGQRM LCTR  
DSECCGDQLCVWGHCTKMATRGSNGTICDNQRDCQPLCCAFQRGLLFPVCTPLPVEGEL  
CHDPASRLLDLITWELEPDGALDRPCASGLLCQPHSHSLVYVCKPTFVGSRDQDGEILL  
PREVPDEYEVGSFMEEVRQELEDLERSLTEEMALGEPAAAAAALLGGEET

**Signal sequence:**

amino acids 1-19

**N-glycosylation site:**

amino acids 96-100, 106-110, 121-125, 204-208

**Casein kinase II phosphorylation site:**amino acids 46-50, 67-71, 98-102, 135-139, 206-210, 312-316,  
327-331**N-myristoylation site:**

amino acids 202-208, 217-223

**Amidation site:**

amino acids 140-144

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**FIGURE 51**

GCCTGTTGCTGATGCTGCCGTGCGGTACTTGTCATGGAGCTGGCACTGCGGCGCTCTCCC  
GTCCCGCGGTGGTTGCTGCTGCTGCCGTGCTGCTGGGCCTGAACGCAGGAGCTGTCATT  
GACTGGCCACAGAGGAGGGCAAGGAAGTATGGGATTATGTGACGGTCCGCAAGGATGCC  
TACATGTTCTGGTGGCTCTATTATGCCACCAACTCCTGCAAGAACTTCTCAGAACTGCCC  
CTGGTCATGTGGCTTCAGGGCGGTCCAGGCGGTTCTAGCACTGGATTGGAACCTTTGAG  
GAAATTGGGCCCCCTTGACAGTGATCTCAAACCACGGAAAAACCACTGGCTCCAGGCTGCC  
AGTCTCCTATTTGTGGATAATCCCGTGGGCACTGGGTTCA GTTATGTGAATGGTAGTGGT  
GCCTATGCCAAGGACCTGGCTATGGTGGCTTCAGACATGATGGTTCCTCTGAAGACCTTC  
TTCAGTTGCCACAAAGAATTCAGACAGTTCATTCTACATTTTCTCAGAGTCCTATGGA  
GGAAAAATGGCAGCTGGCATTGGTCTAGAGCTTTATAAGGCCATTAGCGAGGGGACCATC  
AAGTGCAACTTTGCGGGGGTTGCCTTGGGTGATTCTCGGATCTCCCCTGTTGATTGCGGTG  
CTCTCTGGGGACCTTACCTGTACAGCATGTCTCTTCTCGAAGACAAAGGTCTGGCAGAG  
GTGTCTAAGGTTGCAGAGCAAGTACTGAATGCCGTAAATAAGGGGCTCTACAGAGAGGCC  
ACAGAGCTGTGGGGGAAAGCAGAAATGATCATTGAACAGAACACAGATGGGGTGAACCTTC  
TATAACATCTTAACTAAAAGCACTCCACGTCTACAATGGAGTCGAGTCTAGAATTCACA  
CAGAGCCACCTAGTTTGTCTTTGTGTCAGCGCCACGTGAGACACCTACAACGAGATGCCTTA  
AGCCAGCTCATGAATGGCCCCATCAGAAAGAAGCTCAAAATTTATTCTGAGGATCAATCC  
TGGGGAGGCCAGGCTACCAACGTCTTTGTGAACATGGAGGAGGACTTCATGAAGCCAGTC  
ATTAGCATTGTGGACGAGTTGCTGGAGGCAGGGATCAACGTGACGGTGTATAATGGACAG  
CTGGATCTCATCGTAGATAACCATGGGTCAGGAGGCCTGGGTGCGGAACTGAAGTGGCCA  
GAACTGCCTAAATTCAGTCAGCTGAAGTGAAGGCCCTGTACAGTGACCCTAAATCTTTG  
GAAACATCTGCTTTTGTCAAGTCCTACAAGAACCTTGCTTTCTACTGGATTCTGAAAGCT  
GGTCATATGGTTCCTTCTGACCAAGGGGACATGGCTCTGAAGATGATGAGACTGGTGACT  
CAGCAAGAATAGGATGGATGGGGCTGGAGATGAGCTGGTTTGGCCTTGGGGCACAGAGCT  
GAGCTGAGGCCGCTGAAGCTGTAGGAAGCGCCATTCTTCCCTGTATCTAACTGGGGCTGT  
GATCAAGAAGGTTCTGACCAGCTTCTGCAGAGGATAAAATCATTGTCTCTGGAGGCAATT  
TGGAAATTATTTCTGCTTCTTAAAAAACCTAAGATTTTTTAAAAAATTGATTTGTTTGG  
ATCAAAATAAAGGATGATAATAGATATTA

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**FIGURE 52**

MELALRRSPVPRWLLLLPLLLGLNAGAVIDWPTEEGKEVWDYVTVRKDAYMFWWLYYATN  
SCKNFSELPLVMWLQGGPGGSSTGFGNFEEIGPLDSLKPRKTTWLQAASLLFVDNPVGT  
GFSYVNGSGAYAKDLAMVASDMMVLLKTFFSCHKEFQTVPFYIFSES YGGKMAAGIGLEL  
YKAIQRGTIKCNFAGVALGDSWISPVDSVLSWGPYLYSMSLLEDKGLAEVSKVAEQVLNA  
VNKGLYREATELWGKAEMIEQNTDGVNFYNILTKSTPTSTMESSLEFTQSHLVCLCQRH  
VRHLQRDALSQLMNGPIRKKLKII PEDQSWGGOATNVFVNMEEDFMKPVISIVDELLEAG  
INVTVYNGQLDLIVDTMGQEAWVRKLKWPPELPKFSQLKWKALYSDPKSLETSAFVKSYKN  
LAFYWILKAGHMVPSDQGDMAKMMRLVTQQE

**Signal sequence:**

amino acids 1-25

**N-glycosylation site:**

amino acids 64-68, 126-130, 362-366

**cAMP- and cGMP-dependent protein kinase phosphorylation site:**

amino acids 101-105

**Casein kinase II phosphorylation site:**amino acids 204-208, 220-224, 280-284, 284-288, 351-355,  
449-453**N-myristoylation site:**amino acids 22-28, 76-82, 79-85, 80-86, 119-125, 169-175,  
187-193, 195-201, 331-337, 332-338, 360-366



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**FIGURE 53**

GTCTGTTCCCAGGAGTCCTTCGGCGGCTGTTGTGTCAGTGGCCTGATCGCGATGGGGGACA  
AAGGCGCAAGTCGAGAGGAACTGTTGTGCCTCTTCATATTGGCGATCCTGTTGTGCTCC  
CTGGCATTGGGCAGTGTTACAGTGCACCTCTTCTGAACCTGAAGTCAGAATTCCTGAGAAT  
AATCCTGTGAAGTTGTCTGTGCCTACTCGGGCTTTTCTTCTCCCCGTGTGGAGTGGAAG  
TTTGACCAAGGAGACACCACCAGACTCGTTTGCTATAATAACAAGATCACAGCTTCCTAT  
GAGGACCGGGTGACCTTCTTGCCAACTGGTATCACCTTCAAGTCCGTGACACGGGAAGAC  
ACTGGGACATACACTTGTATGGTCTCTGAGGAAGGCGGCAACAGCTATGGGGAGGTCAAG  
GTCAAGCTCATCGTGCTTGTGCCTCCATCCAAGCCTACAGTTAACATCCCCCTCCTCTGCC  
ACCATTGGGAACCGGGCAGTGCTGACATGCTCAGAACAAGATGGTTCCCCACCTTCTGAA  
TACACCTGGTTCAAAGATGGGATAGTGATGCCTACGAATCCCAAAGCACCCGTGCCTTC  
AGCAACTCTTCCTATGTCTGAATCCACAACAGGAGAGCTGGTCTTTGATCCCCCTGTCA  
GCCTCTGATACTGGAGAATACAGCTGTGAGGCACGGAATGGGTATGGGACACCCATGACT  
TCAAATGCTGTGCGCATGGAAGCTGTGGAGCGGAATGTGGGGGTATCGTGGCAGCCGTC  
CTTGTAACCCTGATTCTCCTGGGAATCTTGGTTTTTGGCATCTGGTTTGCCTATAGCCGA  
GGCCACTTTGACAGAACAAAGAAAGGGACTTCGAGTAAGAAGGTGATTACAGCCAGCCT  
AGTGCCCCGAAGTGAAGGAGAATTCAAACAGACCTCGTCATTCTGCTGGTGTGAGCCTGGTGC  
GCTCACCGCCTATCATCTGCATTTGCCTTACTCAGGTGCTACCGGACTCTGGCCCCCTGAT  
GTCTGTAGTTTACAGGATGCCTTATTTGTCTTCTACACCCACAGGGCCCCCTACTTCT  
TCGGATGTGTTTTTAATAATGTCAGCTATGTGCCCCATCCTCCTTCATGCCCTCCCTCCC  
TTTCCTACCACTGCTGAGTGGCCTGGAACCTTGTTTTAAAGTGTTTTATTCCCCATTTCTTTG  
AGGGATCAGGAAGGAATCCTGGGTATGCCATTGACTTCCCTTCTAAGTAGACAGCAAAAA  
TGGCGGGGGTTCGAGGAATCTGCACTCAACTGCCCACCTGGCTGGCAGGGATCTTTGAAT  
AGGTATCTTGAGCTTGGTTCTGGGCTCTTTCCTTGTGTACTGACGACCAGGGCCAGCTGT  
TCTAGAGCGGGAATTAGAGGCTAGAGCGGCTGAAATGGTTGTTTGGTGATGACACTGGGG  
TCCTTCCATCTCTGGGGCCCACTCTCTTCTGTCTTCCCATGGGAAGTGCCACTGGGATCC  
CTCTGCCCTGTCTCCTGAATACAAGCTGACTGACATTGACTGTGTCTGTGGAAAATGGG  
AGCTCTTGTTGTGGAGAGCATAGTAAATTTTCAGAGAACTTGAAGCCAAAAGGATTTAAA  
ACCGCTGCTCTAAAGAAAAGAAAAGTGGAGGCTGGGCGCAGTGGCTCACGCCTGTAATCC  
CAGAGGCTGAGGCAGGCGGATCACCTGAGGTGCGGAGTTTCGGGATCAGCCTGACCAACAT  
GGAGAAACCCTACTGGAAATACAAAGTTAGCCAGGCATGGTGGTGCATGCCTGTAGTCCC  
AGCTGCTCAGGAGCCTGGCAACAAGAGCAAACTCCAGCTCAAAAAAAAAAAAAAAAAA

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**FIGURE 54**

MGTKAQVERKLLCLFILAILLCSLALGSVTVHSSEPEVRIPENNPVKLS CAYS GFSSPRV  
EWKFDQGD TTRLVCYNNKITASYEDRVTF LPTGITFKSVTREDTGTYTCMVSEEGNSYG  
EVKVKLIVLVPPSKPTVNI PSSATIGNRAVLTCSEQDGSP PSEYTWFKDGIVMPTNPKST  
RAFSNSSYVLNPTTGELVFDPLSASDTGEYSCEARNGYGTPMTSNAVRMEAVERNVGVIV  
AAVLVTLILLGILVFGIWFAYS RGHFDR TKKGTSSKKVIYSQPSARSEGEFKQTSSFLV

**Signal sequence:**

amino acids 1-27

**Transmembrane domain:**

amino acids 238-255

**N-glycosylation site:**

amino acids 185-189

**cAMP- and cGMP-dependent protein kinase phosphorylation site:**

amino acids 270-274

**Casein kinase II phosphorylation site:**amino acids 34-38, 82-86, 100-104, 118-122, 152-156,  
154-158, 193-197, 203-207, 287-291**N-myristoylation site:**amino acids 105-111, 116-122, 158-164, 219-225, 237-243,  
256-262

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**FIGURE 55**

GTTGTGTCCTTCAGCAAAACAGTGGATTAAATCTCCTTGCACAAGCTTGAGAGCAACAC  
AATCTATCAGGAAAGAAAGAAAGAAAAAACCGAACCTGACAAAAAGAAGAAAAAGAAG  
AAGAAAAAAATCATGAAAACCATCCAGCCAAAAATGCACAATTCTATCTCTTGGGCAAT  
CTTACGGGGCTGGCTGCTCTGTGTCTCTTCCAAGGAGTGCCCGTGCGCAGCGGAGATGC  
CACCTTCCCCAAAGCTATGGACAACGTGACGGTCCGGCAGGGGGAGAGCGCCACCTCAG  
GTGCACTATTGACAACCGGGTCACCCGGGTGGCCTGGCTAAACCGCAGCACCATCCTCTA  
TGCTGGGAATGACAAGTGGTGCCTGGATCCTCGCGTGGTCCTTCTGAGCAACACCCAAAC  
GCAGTACAGCATCGAGATCCAGAACGTGGATGTGTATGACGAGGGCCCTTACACCTGCTC  
GGTGCAGACAGACAACCACCCAAAGACCTCTAGGGTCCACCTCATTGTGCAAGTATCTCC  
CAAAATTGTAGAGATTTCTTCAGATATCTCCATTAATGAAGGGAACAATATTAGCCTCAC  
CTGCATAGCAACTGGTAGACCAGAGCCTACGGTTACTTGGAGACACATCTCTCCAAAGC  
GGTTGGCTTTGTGAGTGAAGACGAATACTTGGAAATTCAGGGCATCACCCGGGAGCAGTC  
AGGGGACTACGAGTGCAGTGCCTCCAATGACGTGGCCGCGCCCGTGGTACGGAGAGTAAA  
GGTCACCGTGAACATATCCACCATACATTTCAGAAGCCAAGGGTACAGGTGTCCCGTGGG  
ACAAAAGGGGACACTGCAGTGTGAAGCCTCAGCAGTCCCCTCAGCAGAATTCCAGTGGTA  
CAAGGATGACAAAAGACTGATTGAAGGAAAGAAAGGGGTGAAAGTGGAAAACAGACCTTT  
CCTCTCAAACTCATCTTCTTCAATGTCTCTGAACATGACTATGGGAACTACACTTGCGT  
GGCCTCCAACAAGCTGGGCCACACCAATGCCAGCATCATGCTATTTGGTCCAGGCGCCGT  
CAGCGAGGTGAGCAACGGCACGTGAGGAGGGCAGGCTGCGTCTGGCTGCTGCCTCTTCT  
GGTCTTGACCTGCTTCTCAAATTTTGAATGTGAGTGCCACTTCCCCACCCGGGAAAGGCT  
GCCGCCACCACCACCACCAACACAACAGCAATGGCAACACCGACAGCAACCAATCAGATA  
TATACAAATGAAATTAGAAGAAACACAGCCTCATGGGACAGAAATTTGAGGGAGGGGAAC  
AAAGAATACTTTGGGGGGAAAAGAGTTTAAAAAAGAAATTGAAAATTGCCTTGAGATA  
TTTAGGTACAATGGAGTTTCTTTTCCCAAACGGGAAGAACACAGCACACCCGGCTTGA  
CCCACTGCAAGCTGCATCGTGCAACCTCTTTGGTGCCAGTGTGGGCAAGGGCTCAGCCTC  
TCTGCCCACAGAGTGCCCCACGTGGAACATTCTGGAGCTGGCCATCCCAAATTCATCA  
GTCCATAGAGACGAACAGAATGAGACCTTCCGGCCCAAGCGTGGCGCTGCGGGCACTTTG  
GTAGACTGTGCCACCACGGCGTGTGTTGTGAAACGTGAAATAAAAAGAGCAAAAAAAA

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**FIGURE 56**

MKTIQPKMHNSISWAI FTGLAALCLFQGV PVRSGDATFPKAMD NVTVRQGESATLRCTID  
NRVTRVAWLN RSTILYAGNDKWCLDPRVLLSNTQTQYSIEIQNV DVYDEGPYTCSVQTD  
NHPKTSRVHLIVQVSPKIVEISSDISINEGNNISLT CIATGRPEPTVTWRHISPKAVGFV  
SEDEYLEIQGITREQSGDYEC SASNDVAAPVVRVKVTVNYPPISEAKGTGVPVGQKGT  
LQCEASAVPSAEFQWKDDKRLIEGKKG VKVENRPFLSKLIFFNVSEHDYGN YTCVASNK  
LGHTNASIMLFGPGAVSEVSNGTSRRAGCVWLLPLLVLHLLLKF

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**FIGURE 57**

GCTGCGCCGGCTGCGGCTGCAGGGGAATCCGCTGTGGTGCGGCTGCCAGGCGCGGCCCT  
ACTCGAGTGGCTGGCGCGGGCGCGCTGCGCTCGGACGGCGCGTGCCAGGGGCGCGGGCG  
CCTGCGGGGCGAGGCTCTGGACGCCCTGCGGCCCTGGGACCTGCGCTGCCCTGGGGACGC  
GGCGCAGGAAGAGGAAGAGCTGGAAGAGCGGGCTGTGGCCGGGCCCCGCGCCCCCTCCGCG  
CGGCCCTCCGCGCGGGCCCCGGGGAGGAGCGGGCAGTCGCGCCTTGCCCTCGCGCCTGCGT  
GTGCGTCCCCGAGTCCCGGCACAGCAGCTGCGAGGGGCTGCGGCCTGCAGGCGGTGCCCCG  
CGGCTTCCCCAGCGACACCCAGCTCCTGGACCTGAGGCGGAACCACTTCCCCCTCGGTGCC  
CCGAGCGGCCTTCCCCGNCTGGGCCACCTGGTGTGCTGCACCTGCAGCACTGCGGCAT  
CGCGGAGCTGGAAGCGGGCGCCCTGGCCGGGCTGGGCCGCCTGATCTACCTGTACCTCTC  
CGACAACCAGCTCGCAGGCCTCAGCGCTGCTGCCCTTGAAGGGGCTCCCCGCCTCGGCTA  
CCTGTACCTAGAACGCAACCGTTTCTGTCAGGTGCCAGGGGCTGCCNTGCGCGCCCTGCC  
CAGCCTCTTCTCCCTGCACCTGCAGGACAACGCTGTGGACCGCCTGGCACCTGGGGACCT  
GGGGAGAACACGGGCCTTGCGCTGGGTCTACCTGAGTGGAAACCGCATCACCGAAGTGTC  
CCTTGGGGCGCTGGGGCCAGCTCGGGAGCTGGAGAAGCTGCACCTGGACAGGAATCAGCT  
GCGAGAGGTGCCCACTGGGGCCTTGAGGGGCTGCCTGCCCTCCTGGAGCTGCAGCTCTC  
GGGCAACCCACTCAGGGCCTTGCGTGACGGAGCCTTCCAGCCTGTGGGCAGGTGCTGCA  
GCACCTCTTCTGAAACAGCAGTGGCCTGGAGCAGATTTGTCCTGGGGCCTTTTCAGGCCT  
GGGGCCCCGGGCTCCAGAGCCTGCACCTGCAGAAGAACCAGCTTCGGGGCCCTGCCTGCCCT  
GCCAGTCTCAGCCAGCTGGAGCTCATCGACCTCAGCAGCAATCCCTTCCCCTGTGACTG  
CCAGCTGCTTCCGCTGCACAGGTGGCTTACTGGGCTGAACCTGCGGGTGGGGGCCACCTG  
CGCCACCCCTCCCAATGCCCGTGGCCAGAGGGTGAAGGCTGCAGCTGCTGTCTTTGAAGA  
CTGCCCGGGCTGGGCTGCCAGAAAGGCCAAGCGGACACCAGCCTCCAGGCCCAGTGCCAG  
GAGAACCCCCATCAAAGGAAGACAGTGTGGAGCAGATAAGAACATCCTCTTCCCCACATG  
GTACCACACTGTGGAGCCCACCTCGCTGTCATAGGCCTGCGGCTCTGAAGGATGGCTTTG  
CCCGCTCCCGCTCTGCCCCCTCAAGTGGAACCCAAGCTGGGCTCAGAATCTGTAGAGTGAG  
GCCCCACCAAGGGAACGACACCCACGGCCTGAGAGCCAGGTGGAGTCTGCCACTCAGC  
TGCCTGCCTTTGCTCCCACCCTCTCCCACCCTCAAAGAGGTCTCGAGGGGACACTCTGAA  
GGCACCTGGCTCAGAACCCTGCCATCCAAGGAGCGAGGAGTCCCAGGGCTGAGCAAATG  
CAGCGGGGAGGTGCGCAGTTCCCCTGCTTCCCGATCCTCATTTTCTGCTTCACTTGACTC  
CTCCAGATAGGAGCTGCTCTCACTGCCACACTGCTG

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**FIGURE 58**

LRRLRLQGNPLWCGCQARPLLEWLARARVRSDGACQGPRRLRGEALDALRPWDLRCPGDA  
AQEEEELEERAVAGPRAPPRGPPRGPGEEERAVAPCPACVCVPESRHSSCEGCGLQAVPR  
GFPSDTQLLDLRRNHFPSPRAAFPGLGHLVSLHLQHCGIAELEAGALAGLGRLLIYLYLS  
DNQLAGLSAAALEGAPRLGYLYLERNRFLQVPGAAXRALPSLFSLHLQDNAVDR LAPGDL  
GRTRALRWVYLSGNRITEVSLGALGPARELEKLHLDRNQLREVPTGALEGLPALLELQLS  
GNPLRALRDGAFOQPVGRSLQHLFLNSSGLEQICPGAFSGLGPGLQSLHLQKNQLRALPAL  
PSLSQLELIDLSSNPFPCDCQLLPLHRWLTGLNLRVGATCATPPNARGQQRVKAAA AVFED  
CPGWAARKAKRTPASRPSARRTPIKGRQCGADKNILFPTWYHTVEPTSLS

**Signal sequence:**

None

**Transmembrane domain:**

None

**N-glycosylation site:**

325-328

**Glycosaminoglycan attachment site:**

338-341

**Protein kinase C phosphorylation site:**

438-440

**N-myristoylation site:**

166-171, 186-191, 253-258, 286-291, 335-340, 339-344, 450-455

**Leucine rich repeat N-terminal domain:**

94-123

**Leucine Rich Repeat:**

125-148, 149-172, 173-196, 197-220, 221-244, 245-268, 269-292, 293-316, 318-341, 343-364, 365-386

**Leucine rich repeat C-terminal domain:**

374-422

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**FIGURE 59**

CTCCACGGTGTCCAGCGCCAGAAATGCGGCTTCTGGTCCTGCTATGGGGTTGCCTGCTG  
CTCCAGGTTATGAAGCCCTGGAGGGCCAGAGGAAATCAGCGGGTTCAAGGGGACACT  
GTGTCCCTGCAGTGCACCTACAGGGAAGAGCTGAGGGACACCGGAAGTACTGGTGCAGG  
AAGGGTGGGATCCTCTTCTCTCGCTGCTCTGGCACCATCTATGCAGAAGAAGAAGGCCAG  
GAGACAATGAAGGGCAGGGTGTCCATCCGTGACAGCCGCCAGGAGCTCTCGCTCATTTGTG  
ACCCTGTGGAACCTCACCTTGCAAGACGCTGGGGAGTACTGGTGTGGGGTCGAAAAACGG  
GGCCCCGATGAGTCTTTACTGATCTCTCTGTTTCTCTTTCCAGGACCCTGCTGTCTCTCCC  
TCCCCCTTCTCCACCTTCCAGCCTCTGGCTACAACACGCCTGCAGCCCAAGGCAAAAGCT  
CAGCAAACCCAGCCCCCAGGATTGACTTCTCCTGGGCTCTACCCGGCAGCCACCACAGCC  
AAGCAGGGGAAGACAGGGGCTGAGGCCCCCTCCATTGCCAGGGACTTCCCAGTACGGGCAC  
GAAAGGACTTCTCAGTACACAGGAACCTCTCCTCACCCAGCGACCTCTCCTCCTGCAGGG  
AGCTCCCGCCCCCCCCATGCAGCTGGACTCCACCTCAGCAGAGGACACCAGTCCAGCTCTC  
AGCAGTGGCAGCTCTAAGCCCAGGGTGTCCATCCCGATGGTCCGCATACTGGCCCCAGTC  
CTGGTGTGCTGAGCCTTCTGTGAGCCGAGGCTGATCGCCTTCTGCAGCCACCTGCTC  
CTGTGGAGAAAGGAAGCTCAACAGGCCACGGAGACACAGAGGAACGAGAAGTTCTGGCTC  
TCACGCTTGACTGCGGAGGAAAAGGAAGCCCCCTTCCAGGCCCCCTGAGGGGGACGTGATC  
TCGATGCCTCCCCCTCCACACATCTGAGGAGGAGCTGGGCTTCTCGAAGTTTGTCTCAGCG  
TAGGGCAGGAGGCCCTCCTGGCCAGGCCAGCAGTGAAGCAGTATGGCTGGCTGGATCAGC  
ACCGATTCCCGAAAGCTTTCACCTCAGCCTCAGAGTCCAGCTGCCCGGACTCCAGGGCT  
CTCCCCACCCTCCCCAGGCTCTCCTCTTGATGTTCCAGCCTGACCTAGAAGCGTTTGTCTC  
AGCCCTGGAGCCAGAGCGGTGGCCTTGCTCTTCCGGCTGGAGACTGGGACATCCCTGAT  
AGGTTACATCCCTGGGCAGAGTACCAGGCTGCTGACCCTCAGCAGGGCCAGACAAGGCT  
CAGTGGATCTGGTCTGAGTTTCAATCTGCCAGGAACTCCTGGGCCTCATGCCCAGTGTCTG  
GACCCTGCCTTCTTCCACTCCAGACCCACCTTGTCTTCCCTCCCTGGCGTCTCTCAGAC  
TtagTCCACGGTCTCCTGCATCAGCTGGTGTATGAAGAGGAGCATGCTGGGGTGAGACTG  
GGATTCTGGCTTCTCTTTGAACCACCTGCATCCAGCCCTTCAAGGAAGCCTGTGAAAAACG  
TGATTCTGGCCCCACCAAGACCCACCAAAACCATCTCTGGGCTTGGTGCAGGACTCTGA  
ATTCTAACAATGCCCAGTGACTGTGCACTTGAGTTTGAGGGCCAGTGGGCCTGATGAAC  
GCTCACACCCCTTCACTTAGAGTCTGCATTTGGGCTGTGACGTCTCCACCTGCCCAAT  
AGATCTGCTCTGTCTGCGACACCAGATCCAGTGGGGACTCCCCTGAGGCCTGCTAAGTC  
CAGGCCTTGGTCAAGTCAAGTGCACATTGCAGGATAAGCCCAGGACCGGCACAGAAGTGG  
TTGCCTTTNCCATTTGCCCTCCCTGGNCCATGCCTTCTTGCCCTTTGGAAAAAATGATGAA  
GAAAACCTTGGCTCCTTCTTGTCTGGAAAGGGTTACTTGCCATGGGTTCTGGTGGCTA  
GAGAGAAAAGTAGAAAACAGAGTGCACGTAGGTGTCTAACACAGAGGAGAGTAGGAACA  
GGGCGGATACCTGAAGGTGACTCCGAGTCCAGCCCCCTGGAGAAGGGGTGCGGGGGTGGTG  
GTAAAGTAGCACAACTACTATTTTTTTTCTTTTTCCATTATTATTGTTTTTTAAGACAGA  
ATCTCGTGTGCTGCTGCCCAGGCTGGAGTGCAGTGGCAGCATCTGCAAACCTCCGCCTCCTGG  
GTTCAAGTGATTCTTCTGCCTCAGCCTCCCGAGTAGCTGGGATTACAGGCACGCACCACC  
ACACCTGGCTAATTTTTGTACTTTTAGTAGAGATGGGGTTTACCATTGTTGGCCAGGCTG  
GTCTTGAACCTCCTGACCTCAAATGAGCCTCCTGCTTCACTCTCCCAAATTGCCGGGATTA  
CAGGCATGAGCCACTGTGTCTGGCCCTATTTCTTTTAAAAAGTGAAATTAAGAGTTGTTT  
AGTATGCAAACTTGGAAAGATGGAGGAGAAAAAGAAAAGGAAGAAAAAATGTACCCCA  
TAGTCTCACCAGAGACTATCATTATTTCTGTTTTGTGTACTTCTTCCACTCTTTTCTTC  
TTCACATAATTTGCCGGTGTCTTTTTTACAGAGCAATTATCTTGTATATACAACCTTTGTA  
TCCTGCCTTTTCCACCTTATCGTTCCATCACTTTATTCAGCACTTCTCTGTGTTTTACA  
GACCTTTTTATAAATAAAATGTTTCATCAGCTGCATAAAAAAAAAAAAAA

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**FIGURE 60**

MRLLVLLWGCLLLPGYEALEGPEEISGFEGDTVSLQCTYREELRDHRKYWCRKGGILFSR  
CSGTIYAEEEGQETMKGRVSIRDSRQELSLIVTLWNLTLDAGEYWCGVEKRGPDSELLI  
SLFVFPGPCCPPSPSPPTFQPLATTRLQPKAKAQQTQPPGLTSPGLYPAATTAKQKGTGAE  
APPLPGTSQYGHERTSQYTGTSPHPATSPAGSSRPPMQLDSTSAEDTSPALSSGSSKPR  
VSIPMVRILAPVLVLLSLLSAAGLIAFCSHLLLWRKEAQQATETQORNEKFWLSRLTAEEK  
EAPSQAPEGDVISMPPLHTSEEELGFSKFVSA

**Important features:**

**Signal peptide:**

amino acids 1-17

**Transmembrane domain:**

amino acids 248-269

**N-glycosylation site:**

amino acids 96-99

**Fibrinogen beta and gamma chains C-terminal domain:**

amino acids 104-113

**Ig like V-type domain:**

amino acids 13-128



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**FIGURE 61**

CGGGCCAGCCTGGGGCGGCCGGCCAGGAACCAACCCGTTAAGGTGTCTTCTCTTTAGGGAT  
GGTGAGGTTGGAAAAAGACTCCTGTAACCCCTCCTCCAGGATGAACCACCTGCCAGAAGAC  
ATGGAGAACGCTCTCACCGGGAGCCAGAGCTCCCATGCTTCTCTGCGCAATATCCATTCC  
ATCAACCCACACAACCTCATGGCCAGGATTGAGTCCTATGAAGGAAGGGAAAAGAAAGGC  
ATATCTGATGTCAGGAGGACTTTCTGTTTGTGTTGTCACCTTTGACCTCTTATTCTGTAACA  
TTACTGTGGATAATAGAGTTAAATGTGAATGGAGGCATTGAGAACACATTAGAGAAGGAG  
GTGATGCAGTATGACTACTATTCTTCATATTTTGATATATTTCTTCTGGCAGTTTTTCGA  
TTTAAAGTGTTAATACTTGCATATGCTGTGTGCAGACTGCCCCATTGGTGGGCAATAGCG  
TTGACAACGGCAGTGACCAGTGCCTTTTTACTAGCAAAAGTGATCCTTTTCAAGCTTTTC  
TCTCAAGGGGCTTTTGGCTATGTGCTGCCCATCATTTTCATTATCCTTGCTGGATTGAG  
ACGTGGTTCCTGGATTTCAAAGTGTTACCTCAAGAAGCAGAAGAAGAAAACAGACTCCTG  
ATAGTTCAGGATGCTTCAGAGAGGGCAGCACTTATACCTGGTGGTCTTTCTGATGGTCAG  
TTTTATTCCCCTCCTGAATCCGAAGCAGGATCTGAAGAAGCTGAAGAAAAACAGGACAGT  
GAGAAACCACTTTTAGAACTATGAGTACTACTTTTGTAAATGTGAAAAACCCCTCACAGA  
AAGTCATCGAGGCAAAAAGAGGCAGGCAGTGGAGTCTCCCTGTCGACAGTAAAGTTGAAA  
TGGTGACGTCCACTGCTGGCTTTATTGAACAGCTAATAAAGATTTATTTATTGTAATACC  
TCACAAACGTTGTACCATATCCATGCACATTTAGTTGCCTGCCTGTGGCTGGTAAGGTAA  
TGTCATGATTATCCTCTCTTCAGTGAGACTGAGCCTGATGTGTTAACAAATAGGTGAAG  
AAAGTCTTGCTGTATTCCCTAATCAAAAGACTTAATATATTGAAGTAACACTTTTTTTAG  
TAAGCAAGATACCTTTTTTATTTCAATTCACAGAATGGAATTTTTTTTGTTCATGTCTCAG  
ATTTATTTTGTATTTCTTTTTTAACACTCTACATTTCCCTTGTTTTTTAACTCATGCACA  
TGTGCTCTTTGTACAGTTTTAAAAAGTGTAATAAAATCTGACATGTCAATGTGGCTAGTT  
TTATTTTTCTTGTTTTGCATTATGTGTATGGCCTGAAGTGTTGGACTTGCAAAAGGGGAA  
GAAAGGAATTGCGAATACATGTAAATGTCACCAGACATTTGTATTATTTTTATCATGAA  
ATCATGTTTTTCTCTGATTGTTCTGAAATGTTCTAAATACTCTTATTTTGAATGCACAAA  
ATGACTTAAACCATTCATATCATGTTTCCTTTGCGTTCAGCCAATTTCAATTAAATGAA  
CTAAATTAAAAA

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**FIGURE 62**

MNHLPEDMENALTGSQSSHASLRNIHSINPTQLMARIESYEGREKKGISDVRRTFCLFVT  
FDLLFVTLLWIIELNVNGGIENTLEKEVMQYDYSSYFDIFLLAVFRFKVLILAYAVCRL  
RHWWAIALTTAVTSAFLAKVILSKLFSQGAFGYVLPIISFILAWIETWFLDFKVLQPQA  
EEENRLLIVQDASERAALIPGGLSDGQFYSPPESEAGSEEAEKQDSEKPLLEL

**Important features of the protein:****Signal peptide:**

amino acids 1-20

**Transmembrane domains:**

amino acids 54-72, 100-118, 130-144, 146-166

**N-myristoylation sites:**

amino acids 14-20, 78-84, 79-85, 202-208, 217-223

**FIGURE 63**

CGCCCGGGAGCCCATCTGCCCCACAGGGGCACGGGGGCGGGGGCGGGCTCCCGCCCGGCAC  
ATGGCTGCAGCCACCTCGCGCGCACCCCGAGGCGCCGCGCCAGCTCGCCCGAGGTCCGT  
CGGAGGCGCCCGGCCGCCCGGAGCCAAGCAGCAACTGAGCGGGGAAGCGCCCGCGTCCG  
GGGATCGGGATGTCCTCTCTCTTCTCTCTTGTAGTTTCTACTATGTTGGAACCTTG  
GGGACTCACACTGAGATCAAGAGAGTGGCAGAGGAAAAGTCACTTTGCCCTGCCACCAT  
CAACTGGGGCTTCCAGAAAAAGACACTCTGGATATTGAATGGCTGCTCACCGATAATGAA  
GGGAACCAAAAAGTGGTGATCACTTACTCCAGTCGTCATGTCTACAATAACTTGACTGAG  
GAACAGAAGGGCCGAGTGGCCTTTGCTTCCAATTTCTTGGCAGGAGATGCCTCCTTGCAG  
ATTGAACCTCTGAAGCCAGTGATGAGGGCCGTAACCTGTAAGGTTAAGAATTCAGGG  
CGCTACGTGTGGAGCCATGTCATCTTAAAAGTCTTAGTGAGACCATCCAAGCCCAAGTGT  
GAGTTGGAAGGAGAGCTGACAGAAGGAAGTGACCTGACTTTGCAGTGTGAGTCATCCTCT  
GGCACAGAGCCCATTTGTGTATTACTGGCAGCGAATCCGAGAGAAAGAGGGAGAGGATGAA  
CGTCTGCCTCCCAAATCTAGGATTGACTACAACCACCTTGGACGAGTTCTGCTGCAGAAT  
CTTACCATGTCTTACTCTGGACTGTACCAGTGCACAGCAGGCAACGAAGCTGGGAAGGAA  
AGCTGTGTGGTGCGAGTAACGTACAGTATGTACAAAGCATCGGCATGGTTGCAGGAGCA  
GTGACAGGCATAGTGGCTGGAGCCCTGCTGATTTTCTCTTGGTGTGGCTGCTAATCCGA  
AGGAAAGACAAAAGAAAGATATGAGGAAGAAGAGAGACCTAATGAAATTCGAGAAGATGCT  
GAAGCTCCAAAAGCCCGTCTTGTGAAACCCAGCTCCTCTTCTCAGGCTCTCGGAGCTCA  
CGCTCTGGTTCTTCTCTCACTCGCTCCACAGCAAATAGTGCTTACGCAGCCAGCGGACA  
CTGTCAACTGACGCAGCACCCAGCCAGGGCTGGCCACCAGGCATACAGCCTAGTGGGG  
CCAGAGGTGAGAGGTTCTGAACCAAAAGAAAGTCCACCATGCTAATCTGACCAAAGCAGAA  
ACCACACCCAGCATGATCCCCAGCCAGAGCAGAGCCTTCCAAACGGTCTGAATTACAATG  
GACTTGACTCCCACGCTTTCTTAGGAGTCAGGGTCTTTGGACTCTTCTCGTCATTGGAGC  
TCAAGTCACCAGCCACACAACCAGATGAGAGGTCATCTAAGTAGCAGTGAGCATTTGCAG  
GAACAGATTAGATGAGCATTTTTCTTATACAAATACAAAACAAGCAAAAGGATGTAAGCT  
GATTCATCTGTAAAAGGCATCTTATTGTGCCTTTAGACCAGAGTAAGGGAAAGCAGGAG  
TCCAAATCTATTTGTTGACCAGGACCTGTGGTGAGAAGGTTGGGGAAAGGTGAGGTGAAT  
ATACCTAAAACCTTTTAATGTGGGATATTTTGTATCAGTGCTTTGATTACAAATTTTCAAG  
AGGAAATGGGATGCTGTTTGTAAATTTTCTATGCATTTCTGCAAACCTTATTGGATTATTA  
GTTATTACAGACAGTCAAGCAGAACCCACAGCCTTATTACACCTGTCTACACCATGTACTG  
AGCTAACCACTTCTAAGAACTCCAAAAAAGGAAACATGTGTCTTCTATTCTGACTTAAC  
TTCATTTGTACATAAGGTTTGGATATTAATTTCAAGGGGAGTTGAAATAGTGGGAGATGGA  
GAAGAGTGAATGAGTTTCTCCCACTCTATACTAATCTCACTATTTGTATTGAGCCAAAA  
TAACTATGAAAGGAGACAAAAATTTGTGACAAAGGATTGTGAAGAGCTTTCCATCTTCAT  
GATGTTATGAGGATTGTTGACAAACATTAGAAATATATAATGGAGCAATTGTGGATTTCC  
CCTCAAATCAGATGCCTCTAAGGACTTTCTGCTAGATATTTCTGGAAGGAGAAAAATACA  
ACATGTCATTTATCAACGTCCTTAGAAAGAATTCTTCTAGAGAAAAAGGATCTAGGAAT  
GCTGAAAGATTACCCAACATACCATTATAGTCTCTTCTTTCTGAGAAAAATGTGAAACCAG  
AATTGCAAGACTGGGTGGACTAGAAAGGAGATTAGATCAGTTTTCTCTTAATATGTCAA  
GGAAGGTAGCCGGGCATGGTGCCAGGCACCTGTAGGAAATCCAGCAGGTGGAGGTTGCA  
GTGAGCCGAGATTATGCCATTGCACTCCAGCCTGGGTGACAGAGCGGGACTCCGTCTC

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**FIGURE 64**

MSLLLLLLVSYYVGTLGTHTEIKRVAEEKVTLPCHHQLGLPEKDTLDIEWLLTDNEGNQ  
KVVITYSSRHVYNNLTTEEQKGRVAFASNFLAGDASLQIEPLKPSDEGRYTCKVKNSGRYV  
WSHVILKVLVRPSKPKCELEGELTEGSDLTLQCESSSGTEPIVYYWQRIREKEGEDERLP  
PKSRIDYNHPGRVLLQNLTMSYSGLYQCTAGNEAGKESCVVRVTQYVQSIGMVAGAVTG  
IVAGALLIFLLVWLLIRRKDKERYEEEEERPNEIREDAEAPKARLVKPSSSSSSGSRSSRSG  
SSSTRSTANSASRSQRTLSTDAAPQPGLATQAYSLVGPEVRGSEPCKKVHHANLTKAETTP  
SMIPSQSRAFQTV

**Signal sequence:**  
amino acids 1-16

**Transmembrane domain:**  
amino acids 232-251

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**FIGURE 65**

GTCGGGGCTGCGCGACGGCGCAGGGGCTGCGGGGAGCGCCGCGCAGGCCGTGCAGTTCCT  
AGCGAGGAGGCGCCGCGCCATTGCCGCTCTCTCGGTGAGCGCAGCCCCGCTCTCCGGGC  
CGGGCCTTCGCGGGCCACCGGCGCCATGGGGCCAGTGCGGCATCACCTCCTCCAAGACCGT  
GCTGGTCTTTCTCAACCTCATCTTCTGGGGGGCAGCTGGCATTATGCTATGTGGGAGC  
CTATGCTTTCATCACTTATGATGACTATGACCACTTCTTTGAAGATGTGTACACGCTCAT  
CCCTGCTGTAGTGATCATAGCTGTAGGAGCCCTGCTTTTCATCATTGGGCTAATTGGCTG  
CTGTGCCACAATCCGGGAAAGTCGCTGTGGACTTGCCACGTTTGTATCATCCTGCTCTT  
GGTTTTTGTACAGAAGTTGTTGTAGTGGTTTTTGGGATATGTTTACAGAGCAAAGGTGGA  
AAATGAGGTTGATCGCAGCATTAGAAAGTGTATAAGACCTACAATGGAACCAACCTGA  
TGCTGCTAGCCGGGCTATTGATTATGTACAGAGACAGCTGCATTGTTGTGGAATTCACAA  
CTACTCAGACTGGGAAAATACAGATTGGTTCAAAGAAACCAAAAACCAGAGTGTCCCTCT  
TAGCTGCTGCAGAGAGACTGCCAGCAATTGTAATGGCAGCCTGGCCCACCCTTCCGACCT  
CTATGCTGAGGGGTGTGAGGCTCTAGTAGTGAAGAAGCTACAAGAAATCATGATGCATGT  
GATCTGGGCCCGCACTGGCATTTCAGCTATTTCAGCTGCTGGGCATGCTGTGTGCTTGCAT  
CGTGTGTGTCAGAAGGAGTAGAGATCCTGCTTACGAGCTCCTCATCACTGGCGGAACCTA  
TGCATAGTTGACAACCTCAAGCCTGAGCTTTTTTGGTCTTGTTCTGATTGGAAGGTGAATT  
GAGCAGGTCTGCTGCTGTTGGCCTCTGGAGTTCATTTAGTTAAAGCACATGTACACTGGT  
GTTGGACAGAGCAGCTTGGCTTTTCATGTGCCCACCTACTTACCTACTACCTGCGACTTT  
CTTTTTCCTTGTTCTAGCTGACTCTTCATGCCCTAAGATTTTAAGTACGATGGTGAACG  
TTCTAATTTTCAAGCAATTCGAGTCATGTAGTGTGGTAGAATTAAAGGAGGACACGAG  
CCTGCTTCTGTTACCTCCAAGTGGTAACAGGACTGATGCCGAAATGTCACCAGGTCCCTT  
CAGTCTTCACAGTGGAGAACTCTTGGCCAAAGGTTTTTGGGGGAGGAGGAGGAAACCAG  
CTTTCTGGTTAAGGTTAACACCAGATGGTGCCCCTCATTGGTGTCTTTTAAAAAATATT  
TACTGTAGTCCAATAAGATAGCAGCTGTACAAAATGACTAAAATAGATTGTAGGATCATA  
TGGCGTATATCTTGGTTTCATCTTCAAAATCAGAGACTGAGCTTTGAAACTAGTGGTTTTT  
AATCAAAGTTGGCTTTATAGGAGGAGTATAATGTATGCACTACTGTTTTAAAGAATTAG  
TGTGAGTGTGTTTTTGTATGAATGAGCCCATTCATGGTAAGTCTTAAGCTTGTGGAAAT  
AATGTACCCATGTAGACTAGCAAAATAGTATGTAGATGTGATCTCAGTTGTAAATAGAAA  
AATCTAATTCAATAAACTCTGTATCAGCCCCCAAAAAAAAAAAAAAAAAA

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**FIGURE 66**

MGQCGITSSKTVLVFLNLI FWGAAGILCYVGAYVFITYDDYDHFEDVYTLIPAVVIIAV  
GALLFIIGLIGCCATIRESRCGLATFVIIILLVVFTEVVVVVLGYVYRAKVENEVDRSIQ  
KVYKTYNGTNPDAASRAIDYVQRQLHCCGIHNYSDWENTDWFKETKNQSVPLSCCRETAS  
NCNGSLAHPSDLYAEGCEALVVKKLQEIMMHVIWAALAFAAIQLLGMLCACIVLCRRSRD  
PAYELLITGGTYA

**Signal peptide:**

none

**Type II transmembrane domain:**

11-38

**Other transmembrane domains:**

48-68, 87-107, 208-235

**N-glycosylation site:**

127-131, 152-156, 167-171, 183-187

**Tyrosine kinase phosphorylation site:**

236-244

**N-myristoylation site:**

5-11, 68-74, 71-77, 226-232

**Prokaryotic membrane lipoprotein lipid attachment site:**

62-73, 221-232

**Transmembrane 4 family proteins:**

7-35, 56-106

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**FIGURE 67**

GCGGCACCTGGAAGATGCGCCCATTTGGCTGGTGGCCTGCTCAAGGTGGTGTTCGTGGTCT  
TCGCCTCCTTGTGTGCCTGGTATTTCGGGGTACCTGCTCGCAGAGCTCATTCAGATGCAC  
CCCTGTCCAGTGCTGCCTATAGCATCCGCAGCATCGGGGAGAGGCCTGTCCTCAAAGCTC  
CAGTCCCCAAAAGGCAAAAATGTGACCACTGGACTCCCTGCCCATCTGACACCTATGCCT  
ACAGGTTACTCAGCGGAGGTGGCAGAAGCAAGTACGCCAAAATCTGCTTTGAGGATAACC  
TACTTATGGGAGAACAGCTGGGAAATGTTGCCAGAGGAATAAACATTGCCATTGTCAACT  
ATGTAACTGGGAATGTGACAGCAACACGATGTTTTGATATGTATGAAGGCGATAACTCTG  
GACCGATGACAAAGTTTATTCAGAGTGCTGCTCCAAAATCCCTGCTCTTCATGGTGACCT  
ATGACGACGGAAGCACAAGACTGAATAACGATGCCAAGAATGCCATAGAAGCACTTGGAA  
GTAAAGAAATCAGGAACATGAAATTTCAGGTCTAGCTGGGTATTTATTGCAGCAAAAGGCT  
TGGAACTCCCTTCCGAAATTCAGAGAGAAAAGATCAACCACTCTGATGCTAAGAACACA  
GATATTCTGGCTGGCCTGCAGAGATCCAGATAGAAGGCTGCATACCCAAAGAACGAAGCT  
GCACTGCAGGGTCCTGAGTAAATGTGTTCTGTATAAACAAATGCAGCTGGAATCGCTCA  
AGAATCTTATTTTCTAAATCCAACAGCCCATATTTGATGAGTATTTTGGGTTTGTGTA  
AACCAATGAACATTTGCTAGTTGTATCAAATCTTGGTACGCAGTATTTTATACCAGTAT  
TTTATGTAGTGAAGATGTCAATTAGCAGGAACTAAAATGAATGGAAATTC'TAAAAAAA  
AAA

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**FIGURE 68**

MRPLAGGLLKVVVFVVFASLCAWYSGYLLAELIPDAPLSSAAYSIRSIGERPVLKAPVPKR  
QKCDHWTPCPSDTYAYRLLSGGGRSKYAKICFEDNLLMGEQLGNVARGINIAIVNYVTGN  
VTATRCFDMYEGDNSGPMTKFIQSAAPKSLLFMVTYDDGSTRLNNDAKNAIEALGSKEIR  
NMKFRSSWVFIAAKGLELPSEIQREKINHSDAKNNRYSGWPAEIQIEGCI PKERS

**Signal sequence:**

amino acids 1-20

**N-glycosylation sites:**

amino acids 120-124, 208-212

**Glycosaminoglycan attachment site:**

amino acids 80-84

**N-myristoylation sites:**

amino acids 81-87, 108-114, 119-125



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**FIGURE 69**

ACACAACCTTTACACCTGAATGAACGCCAAACCTCTATGGATATATAAAGGGAAGCTTGAG  
GAGGAATTTTACAGTTACAGTGCAGAAGCAGAAGCAAAGAATTAACCAGCTCTTCAGTC  
AAGCAAATCCTCTACTCACCATGCTTCCTCCTGCCATTCAATTCCTATCTCCTTCCCCTTG  
CATGCATCCTAATGAAAAGCTGTTTGGCTTTTAAAAATGATGCCACAGAAATCCTTTATT  
CACATGTGGTTAAACCTGTTCCAGCACACCCCAGCAGCAACAGCACGTTGAATCAAGCCA  
GAAATGGAGGCAGGCATTTTCAGTAACACTGGACTGGATCGGAACACTCGGGTTCAAGTGG  
GTTGCCGGGAACTGCGTTCCACCAAATACATCTCTGATGGCCAGTGCACCAGCATCAGCC  
CTCTGAAGGAGCTGGTGTGTGCTGGCGAGTGCTTGCCCCTGCCAGTGCTCCCTAACTGGA  
TTGGAGGAGGCTATGGAACAAAGTACTGGAGCAGGAGGAGCTCCCAGGAGTGGCGGTGTG  
TCAATGACAAAACCCGTACCCAGAGAATCCAGCTGCAGTGCCAAGATGGCAGCACACGCA  
CCTACAAAATCACAGTAGTCACTGCCTGCAAGTGCAAGAGGTACACCCGGCAGCACAAACG  
AGTCCAGTCACAACCTTTGAGAGCATGTACCTGCCAAGCCAGTCCAGCATCACAGAGAGC  
GGAAAAGAGCCAGCAAATCCAGCAAGCACAGCATGAGTTAGAACTCAGACTCCCATAACT  
AGACTTACTAGTAACCATCTGCTTTACAGATTTGATTGCTTGGAAGACTCAAGCCTGCCA  
CTGCTGTTTTTCTCACTTGAAAGTATATGCTTTCTGCTTTGATCAAACCCAGCAAGCTGTC  
TTAAGTATCAGGACCTTCTTTGGGAATAGTTTTTCTTTTAAAGTTTTTCAAGATGTAGG  
TATATCCATGAATGCAATTTGCATTTAAATTCACGTATCCCTGTAGTTTAAATTCCTCA  
TTGGTCTTAAAAGACTGTTGATACTATAAACATCAGTGGAATCAATTATATTTTAAACA  
GAAAAGGGCTT

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**FIGURE 70**

MLPPAIHFYLLPLACILMKSCLA FKNDAT EILYSHVVKPVP AHPSSNSTLNQARNGGRHF  
SNTGLDRNTRVQVGCRELRSTKYISDGQCTSI SPLKELVCAGECLPLPVL PNWIGGGYGT  
KYWSRRSSQEWRCVNDKTRTQRIQLQCQDGSTR TYKITVVTACKCKRYTRQHNESSHNFE  
SMSPAKPVQHHREKRASKSSKHSMS

**Signal sequence:**

1-23

**Transmembrane domain:**

None

**N-glycosylation site:**

47-50, 173-176

**cAMP- and cGMP-dependent protein kinase phosphorylation site:**

125-128, 166-169, 195-198

**N-myristoylation site:**

64-69, 87-92, 115-120, 116-121, 150-155

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**FIGURE 71**

CCCAGGCTCTAGTGCAGGAGGAGAAGGAGGAGGAGCAGGAGGTGGAGATTCCCAGTTAAA  
AGGCTCCAGAATCGTGTACCAGGCAGAGAACTGAAGTACTGGGGCCTCCTCCACTGGGTC  
CGAATCAGTAGGTGACCCCGCCCCCTGGATTCTGGAAGACCTCACCATGGGACGCCCCCGA  
CCTCGTGCGGCCAAGACGTGGATGTTCTTGCTCTTGCTGGGGGGAGCCTGGGCAGGACAC  
TCCAGGGCACAGGAGGACAAGGTGCTGGGGGGTCAAGAGTGCCAACCCCATTCGCAGCCT  
TGGCAGGCGGCCTTGTTCCAGGGCCAGCAACTACTCTGTGGCGGTGTCCTTGTAAGTGGC  
AACTGGGTCTTACAGCTGCCCCACTGTAAAAAACCGAAATACACAGTACGCCTGGGAGAC  
CACAGCCTACAGAATAAAGATGGCCCAGAGCAAGAAATACCTGTGGTTCAGTCCATCCCA  
CACCCCTGCTACAACAGCAGCGATGTGGAGGACCACAACCATGATCTGATGCTTCTTCAA  
CTGCGTGACCAGGCATCCCTGGGGTCCAAAGTGAAGCCCATCAGCCTGGCAGATCATTGC  
ACCCAGCCTGGCCAGAAGTGACCGTCTCAGGCTGGGGCACTGTCACCAAGTCCCCGAGAG  
AATTTTCTTGACACTCTCAACTGTGCAGAAGTAAAAATCTTTCCCCAGAAGAAGTGTGAG  
GATGCTTACCCGGGGCAGATCACAGATGGCATGGTCTGTGCAGGCAGCAGCAAAGGGGCT  
GACACGTGCCAGGGCGATTCTGGAGGCCCCCTGGTGTGTGATGGTGCCTCCAGGGCATC  
ACATCCTGGGGCTCAGACCCCTGTGGGAGGTCCGACAAACCTGGCGTCTATACCAACATC  
TGCCGCTACCTGGACTGGATCAAGAAGATCATAGGCAGCAAGGGCTGATTTCTAGGATAAG  
CACTAGATCTCCCTTAATAAACTCACAACTCTCTGGTTC

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**FIGURE 72**

MGRPRPRAAKTWMFLLLLGGAWAGHSRAQEDKVLGGHECQPHSQPWQAALFQGQQLLCGG  
VLVGGNWVLTAAHCKKPKYTVRLGDHSLQNKDGPEQEIPVVQSI PHPCYNSSDVEDHNHD  
LMLLQLRDQASLGSKVKPISLADHCTQPGQKCTVSGWGTVTSPRENFPDTLNCAEVKIFP  
QKKCEDAYPGQITDGMVCAGSSKGADTCQGDSSGGLVCDGALQGITSWGSDPCGRSDKPG  
VYTNICRYLDWIKKIIGSKG

**Important Features:****Signal peptide:**

amino acids 1-23

**Transmembrane domain:**

amino acids 51-71

**N-glycosylation site:**

amino acids 110-113

**Serine proteases, trypsin family, histidine active site:**

amino acids 69-74 and 207-217

**Tyrosine kinase phosphorylation site:**

amino acids 182-188

**Kringle domain proteins motif:**

amino acids 205-217

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**FIGURE 73**

CTCGGGCGCGCACAGGCAGCTCGGTTTGGCCCTGCGATTGAGCTGCGGGTTCGCGGCCGGCG  
CCGGCCTCTCCAATGGCAAATGTGTGTGGCTGGAGGCGAGCGCGAGGCTTTTCGGCAAAGG  
CAGTCGAGTGTTTGCAGACCGGGGCGAGTCTGTGAAAGCAGATAAAAGAAAACATTTAT  
TAACGTGTCAATTACGAGGGGAGCGCCCGGGCGGGGCTGTGCACTCCCCGCGGAACATTT  
GGCTCCCTCCAGCTCCGAGAGAGGAGAAGAAGAAAGCGGAAAAGAGGCAGATTCACGTCTG  
TTTCCAGCCAAGTGGACCTGATCGATGGCCCTCCTGAATTTATCACGATATTTGATTTAT  
TAGCGATGCCCCCTGGTTTGTGTGTACGCACACACACGTGCACACAAGGCTCTGGCTCG  
CTTCCCTCCCTCGTTTCCAGCTCCTGGGCGAATCCACATCTGTTTCAACTCTCCGCCGA  
GGGCGAGCAGGAGCGAGAGTGTGTGGAATCTGCGAGTGAAGAGGGACGAGGGGAAAAGAAA  
CAAAGCCACAGACGCAACTTGAGACTCCCGCATCCCAAAGAAGCACCAGATCAGCAAAA  
AAAGAAGATGGGCCCCCGAGCCTCGTGCTGTGCTTGTGTCCGCAACTGTGTTCTCCCT  
GCTGGGTGGAAGCTCGGCCCTTCTGTGCGACCAACCGCTGAAAGGCAGGTTTCAGAGGGA  
CCGCAGGAACATCCGCCCAACATCATCCTGGTGCTGACGGACGACCAAGGATGTGGAGCT  
GGGTTCCATGCAGGTGATGAACAAGACCGGCGCATCATGGAGCAGGGCGGGGCGCACTT  
CATCAACGCCTTCGTGACCACACCCATGTGCTGCCCTCACGCTCCTCCATCCTCACTGG  
CAAGTACGTCCACAACCACAACACCTACACCAACAATGAGAAGTGTCTCTCGCCCTCCTG  
GCAGGCACAGCACGAGAGCCGCACCTTTGCCGTGTACCTCAATAGCACTGGCTACCGGAC  
AGCTTTCCTTCGGGAAGTATCTTAATGAATACAACGGCTCCTACGTGCCACCGGCTGGAA  
GGAGTGGGTTCGACTCCTTAAAACTCCCGCTTTTATAACTACAGCTGTGTTCGGAACGG  
GGTGAAGAGAAAGCACGGCTCCGACTACTCCAAGGATTACCTCACAGACCTCATACCAA  
TGACAGCGTGAGCTTCTTCGCGACGTCCAAGAAGATGTACCCGCACAGGCCAGTCTCAT  
GGTCATCAGCCATGCAGCCCCCACGGCCCTGAGGATTAGCCCCACAATATTCACGCCT  
CTTCCCAAACGCATCTCAGCACATCACGCCGAGCTACAACTACGCGCCCAACCCGGACAA  
ACACTGGATCATGCGCTACACGGGGCCCATGAAGCCCATCCACATGGAATTCACCAACAT  
GCTCCAGCGGAAGCGCTTGACAGCCCTCATGTGCGTGGACGACTCCATGGAGACGATTTA  
CAACATGCTGGTTGAGACGGGCGAGCTGGACAACACGTACATCGTATACACCGCCGACCA  
CGGTTACCACATCGGCCAGTTTGGCCTGGTGAAGGGGAAATCCATGCCATATGAGTTTGA  
CATCAGGGTCCCGTTCTACGTGAGGGGCCCCAACGTGGAAGCCGGCTGTCTGAATCCCCA  
CATCGTCTCAACATTGACCTGGCCCCCACCATCCTGGACATTGCAGGCCTGGACATACC  
TGCGGATATGGACGGGAAATCCATCCTCAAGCTGTGACACGGAGCGGCCGGTGAATCG  
GTTTCACTTGAAAAAGAAGATGAGGGTCTGGCGGGACTCCTTCTTGGTGGAGAGAGGCAA  
GCTGTACACAAGAGAGACAATGACAAGGTGGACGCCCAGGAGGAGAACTTCTGCCCCAA  
GTACCAGCGTGTGAAGGACCTGTGTGACCGTGTGAGTACCAGACGGCGTGTGAGCAGCT  
GGGACAGAAGTGGCAGTGTGTGGAGGACGCCACGGGGAAGCTGAAGCTGCATAAGTGCAA  
GGGCCCCATGCGGTGGGCGGCAGCAGAGCCCTCTCCAACCTCGTGCCCAAGTACTACGG  
GCAGGGCAGCGAGGCCTGCACCTGTGACAGCGGGGACTACAAGCTCAGCCTGGCCGGACG  
CCGAAAAAACTCTTCAAGAAGAAGTACAAGGCCAGCTATGTCCGCAGTCGCTCCATCCG  
CTCAGTGGCCATCGAGGTGGACGGCAGGGTGTACCACGTAGGCCTGGGTGATGCCGCCCA  
GCCCCGAAACCTCACCAAGCGGCACTGGCCAGGGGCCCCCTGAGGACCAAGATGACAAGGA  
TGGTGGGGACTTCAGTGGCACTGGAGGCCTTCCCGACTACTCAGCCGCCAACCCATTAA  
AGTGACACATCGGTGCTACATCCTAGAGAACGACACAGTCCAGTGTGACCTGGACCTGTA  
CAAGTCCCTGCAGGCCTGGAAAGACCACAAGCTGCACATCGACCACGAGATTGAAACCCCT  
GCAGAACAAAATTAAGAACCTGAGGGAAGTCCGAGGTACCTGAAGAAAAAGCGGCCAGA  
AGAATGTGACTGTCAAAAATCAGCTACCACACCCAGCACAAAGGCCGCCTCAAGCACAG  
AGGCTCCAGTCTGCATCCTTTCAGGAAGGGCCTGCAAGAGAAGGACAAGGTGTGGCTGTT  
GCGGGAGCAGAAGCGCAAGAAGAACTCCGCAAGCTGCTCAAGCGCCTGCAGAACCAACGA  
CACGTGCAGCATGCCAGGCCTCACGTGCTTACCCACGACAACCAGCACTGGCAGACGGC

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GCCTTTCTGGACACTGGGGCCTTTCTGTGCCTGCACCAGCGCCAACAATAACACGTA CTG  
GTGCATGAGGACCATCAATGAGACTCACAATTCCTCTTCTGTGAATTTGCAACTGGCTT  
CCTAGAGTACTTTGATCTCAACACAGACCCCTACCAGCTGATGAATGCAGTGAACACACT  
GGACAGGGATGTCCTCAACCAGCTACACGTACAGCTCATGGAGCTGAGGAGCTGCAAGGG  
TTACAAGCAGTGTAACCCCCGGACTCGAAACATGGACCTGGATGGAGGAAGCTATGAGCA  
ATACAGGCAGTTTCAGCGTCGAAAGTGGCCAGAAATGAAGAGACCTTCTTCCAAATCACT  
GGGACAACTGTGGGAAGGCTGGGAAGGTTAAGAAACAACAGAGGTGGACCTCCAAAAACA  
TAGAGGCATCACCTGACTGCACAGGCAATGAAAAACCATGTGGGTGATTTCCAGCAGACC  
TGTGCTATTGGCCAGGAGGCCTGAGAAAGCAAGCACGCACTCTCAGTCAACATGACAGAT  
TCTGGAGGATAACCAGCAGGAGCAGAGATAACTTCAGGAAGTCCATTTTTTGCCCCTGCTT  
TTGCTTTGGATTATACCTCACCAGCTGCACAAAATGCATTTTTTTCGTATCAAAAAGTCAC  
CACTAACCCCTCCCCAGAAGCTCACAAAGGAAAACGGAGAGAGCGAGCGAGAGAGATTTC  
CTTGGAATTTCTCCCAAGGGCGAAAAGTCATTGGAATTTTAAATCATAGGGGAAAAGCA  
GTCCTGTTCTAAATCCTCTTATTCTTTTGGTTTGTACAAAGAAGGAACCTAAGAAGCAGG  
ACAGAGGCAACGTGGAGAGGCTGAAAACAGTGCAGAGACGTTTGACAATGAGTCAGTAGC  
ACAAAAGAGATGACATTTACCTAGCACTATAAACCTGGTTGCCTCTGAAGAACTGCCT  
TCATTGTATATATGTGACTATTTACATGTAATCAACATGGGAACCTTTAGGGGAACCTAA  
TAAGAAATCCCAATTTTCAGGAGTGGTGGTGTCAATAAACGCTCTGTGGCCAGTGTA AAA  
GAAAAA

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**FIGURE 74**

MGPPSLVLCLLSATVFSLLGGSSAFLSHHRLKGRFQDRRNIRPNIIIVLTDDQDVELGS  
MQVMNKTRRIMEQGGAHFINAFVTTMCCPSRSSILTGKYVHNHNTYTNNECCSSPSWQA  
QHESTRFAVYLNSTGYRTAFFGKYLNEYNGSYVPPGWKEWVGLLKNSRFYNYTLCRNGVK  
EKHGS DY SKDYLTDLITNDSVSFFRTSKKMPHRPVLMVISHAAPHGPEDSAPQYSRLFP  
NASQHITPSYNYAPNPDKHWIMRYTGPMKPIHMEFTNMLQRKRLQTLMSVDDSMETIYNM  
LVETGELDNTYIVYTADHGYHIGQFGLVKGKSMPYEFDIRVPFYVRGPNVEAGCLNPHIV  
LNIDLAPTILDIAGLDIPADMDGKSILKLLDTERPVNRFHLKKKMRVWRDSFLVERGKLL  
HKRDNDKVDAQEENFLPKYQRVKDLQRAEYQTACEQLGQKWQCVEDATGKLKHLKCKGP  
MRLGGSRALSNLVPKYQGSEACTCDSGDYKLSLAGRRKKLFKKKYKASYVRSRSIRSV  
AIEVDGRVYHVGLGDAAQPRNLTKRHWPGAPEDQDDKDGDFSGTGGLPDYSAANPIKVT  
HRCYILENDTVQCDLDLYKSLQAWKDHKLHIDHEIETLQNKIKNLREVRGHLKKKRPEEC  
DCHKISYHTQHKGRCLKHRGSSLHPFRKGLQEKDKVWLLREQKRKKKLRKLLKRLQNNDT  
SMPGLTCFTHDNQHWQTAPFWTLGPFCACTSANNNTYWCMRTINETHNLFCEFATGFLE  
YFDLNTDPYQLMNAVNTLDRDVLNQLHVQLMELRSCKGYKQCNPRTRNMDLDGGSYEQYR  
QFQRRKWPEMKRPSSKSLGQLWEGWEG

**Important features:****Signal peptide:**

amino acids 1-17

**Sulfatases signature 1:**

amino acids 86-99

**Homologous region to sulfatase:**

amino acids 87-106, 133-146, 216-229, 291-320, 365-375

**N-glycosylation sites:**amino acids 65-69, 112-116, 132-136, 149-153, 171-175,  
198-202, 241-245, 561-565, 608-612, 717-721, 754-758,  
764-768

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**FIGURE 75**

CCCACGCGTCCGCCACGCGTCCGGTGGACTATGGGCCAGTTTTTGTGCAAGAACCAGAT  
GATATTATTTTTCCAAGTATTCTGATGAAAAGAAGGTAGCATTGAATTGTGAAGTTCGT  
GGCAATCCAGTTCAGTTACAGATGGCTTCGAAATGGAACAGAAATAGATCTGGAAAGT  
GATTATCGCTACAGTTTGATAGATGGCACCTTCATTATAAGCAATCCAAGTGAAGCAAAG  
GATTCTGGTCATTATCAGTGTGTAGCAACCAACACTGTGGGGAGTATTCTTAGTAGAGAA  
GCTACACTGCAGTTTGCCTATCTGGGAAATTTTAGTGGCCGACAGAAGTGCAGTCTCT  
GTGAGGGAAGGCCAGGGTGTCTGTTCTGATGTGCTCTCCTCCGCCACATTCACCAGAGATC  
ATCTATAGCTGGGTATTTAATGAGTTCCTTCTCTTGTGGCGGAAGACAGCCGGCGGTTT  
ATCTCCAGGAGACAGGCAACCTTTATATTTCTAAAGTCCAAACATCAGATGTTGGCAGC  
TATATTTGTCTGGTGAAAAACACAGTGACGAATGCTAGAGTCCTTAGTCCTCCAACGCCA  
CTCACTCTGCGTAATGATGGTGTGATGGGAGAATATGAGCCGAAAATTGAGGTCCATTTT  
CCTTTCACGGTTACAGCTGCTAAAGGAACAACCTGTTAAGATGGAATGCTTTGCACTTGGC  
AACCCCGTTCCAACAATCACATGGATGAAGGTTAATGGTTATATTCCTAGTAAGGCACGT  
CTGCGGAAATCTCAGGCGGTGCTGGAAATACCGAATGTACAGCTGGATGATGCAGGCATT  
TATGAGTGCAGAGCTGAAAACCTCAGTGGAATAATTCCTTTCGTGGACAATTACAAGTA  
TACACCTACCCACACTGGGTAGAAAACTGAATGATACTCAGTTAGACAGTGGGAGCCCT  
CTCCGATGGGAATGTAAGGCTACTGGAAAACCCAGACCCACGTATCGTTGGCTGAAGAAT  
GGAGTACCCCTCTCACCTCAGAGTAGGGTTGAGATGGTTAATGGAGTATTGATGATCCAC  
AATGTGAATCAATCAGATGCTGGAATGTATCAGTGTGTGGCTGAAAATAAGTATGGAGCC  
ATTTACGCTAGTGCTGAGCTGAAGATTCTAGCTTCAGCTCCCACTTTTGCACTGAATCAA  
CTGAAGAAAACAATAATTGTTACCAAAGACCAAGAAGTTGTCATAGAGTGCAAACCCCAA  
GGCTCTCCAAAACCAACCATCTCTTGGAAGAAAGGAGACAGAGCAGTTAGAGAAAACAAA  
AGAATAGCTATTCTTCCAGACGGGAGTCTACGGATCCTAAATGCTTCCAAATCAGACGAG  
GGAAAGTACGTTTGCCGAGGGGAAAACGTCTTTGGTTCTGCTGAAAT



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**FIGURE 76**

MCSPPPHSPEIIYSWVFNEFPSFVAEDSRRFISQETGNLYISKVQTS DVGSIYICLVKNTV  
TNARVLSPTPLTLRNDGVMGEYEPKIEVHFPTVTAAGTTVKMECFALGNPVPTITWM  
KVNGYIPSKARLRKSQAVLEIPNVQLDDAGIYECRAENSRGKNSFRGQLQVYTYPHWVEK  
LNDTQLDSGSPLRWECKATGKPRPTYRWLKNGVPLSPQSRVEMVNGVLMIHNVNQSDAGM  
YQCLAENKYGAIYASAE LKILASAPTFALNQLKKTIIIVTKDQEVVIECKPQGSPKPTISW  
KKGDRAVRENKRIAILPDGSLRILNASKSDEGKYVCRGENVFGSAE

**Signal sequence:**

None

**Transmembrane domain:**

None

**N-glycosylation site:**

182-185, 234-237, 325-328

**Tyrosine kinase phosphorylation site:**

328-334

**N-myristoylation site:**

50-55, 150-155, 239-244, 250-255

**Immunoglobulin domain:**

2-56, 100-156, 189-245, 281-338

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## FIGURE 77

GCTCCCAGCCAAGAACCTCGGGGCCGCTGCGCGGTGGGGAGGAGTTCCCCGAAACCCGGC  
CGCTAAGCGAGGCCTCCTCCTCCCGCAGATCCGAACGGCCTGGGCGGGGTACCCCCGGCT  
GGGACAAGAAGCCCGCCGCTGCCTGCCCGGGCCCGGGAGGGGGCTGGGGCTGGGGCCGG  
AGGCGGGGTGTGAGTGGGTGTGTGCGGGGGCGGAGGCTTGATGCAATCCCGATAAGAAA  
TGCTCGGGTGTCTTGGGCACCTACCCGTGGGGCCCGTAAGGCGCTACTATATAAGGCTGC  
CGGCCCCGAGCCCGCCGCGCGTCAGAGCAGGAGCGCTGCGTCCAGGATCTAGGGCCACGA  
CCATCCCAACCCGGCACTCACAGCCCCGCAGCGCATCCCGGTGCGCGCCAGCCTCCCCG  
ACCCCATCGCCGGAGCTGCGCCGAGAGCCCCAGGGAGGTGCCATGCGGAGCGGGTGTGT  
GGTGGTCCACGTATGGATCCTGGCCGGCCTCTGGCTGGCCGTGGCCGGGCGCCCCCTCGC  
CTTCTCGGACGCGGGGCCCCACGTGCACTACGGCTGGGGCGACCCCATCCGCCTGCGGCA  
CCTGTACACCTCCGGCCCCACGGGCTCTCCAGCTGCTTCTGCGCATCCGTGCCGACGG  
CGTCGTGGACTGCGCGCGGGGCCAGAGCGCGCACAGTTTGCTGGAGATCAAGGCAGTCGC  
TCTGCGGACCGTGGCCATCAAGGGCGTGACAGCGTGCGGTACCTCTGCATGGGCGCCGA  
CGGCAAGATGCAGGGGTGCTTCAGTACTCGGAGGAAGACTGTGCTTTTCGAGGAGGAGAT  
CCGCCCAGATGGCTACAATGTGTACCGATCCGAGAAGCACCGCCTCCCGGTCTCCCTGAG  
CAGTGCCAAACAGCGGCAGCTGTACAAGAACAGAGGCTTTCTTCCACTCTCTCATTTCT  
GCCCATGCTGCCCATGGTCCCAGAGGAGCCTGAGGACCTCAGGGGCCACTTGGAATCTGA  
CATGTTCTCTTCGCCCCCTGGAGACCGACAGCATGGACCCATTTGGGCTTGTCACCGGACT  
GGAGGCCGTGAGGAGTCCCAGCTTTGAGAAGTAACTGAGACCATGCCCGGGCCTCTTCAC  
TGCTGCCAGGGGCTGTGGTACCTGCAGCGTGGGGGACGTGCTTCTACAAGAACAGTCCTG  
AGTCCACGTTCTGTTTAGCTTTAGGAAGAAACATCTAGAAGTTGTACATATTCAGAGTTT  
TCCATTGGCAGTGCCAGTTTCTAGCCAATAGACTTGTCTGATCATAACATTGTAAGCCTG  
TAGCTTGCCCAGCTGCTGCCCTGGGCCCCCATTCTGCTCCCTCGAGGTTGCTGGACAAGCT  
GCTGCACTGTCTCAGTTCTGCTTGAATACCTCCATCGATGGGGAACCTCACTTCCTTTGGA  
AAAATTCTTATGTCAAGCTGAAATTCCTAATTTTTTCTCATCACTTCCCCAGGAGCAGC  
CAGAAGACAGGCAGTAGTTTTAATTTAGGAACAGGTGATCCACTCTGTAAACAGCAGG  
TAAATTTCACTCAACCCCATGTGGGAATTGATCTATATCTCTACTTCCAGGGACCATTG  
CCCTTCCCAAATCCCTCCAGGCCAGAACTGACTGGAGCAGGCATGGCCCACCAGGCTTCA  
GGAGTAGGGGAAGCCTGGAGCCCCACTCCAGCCCTGGGACAACTTGAGAATTCCCCCTGA  
GGCCAGTTCTGTCAATGGATGCTGTCTGAGAATAACTTGCTGTCCCGGTGTCACCTGCTT  
CCATCTCCAGCCCACCAGCCCTCTGCCACCTCACATGCCTCCCCATGGATTGGGGCCT  
CCCAGGCCCCCACCTTATGTCAACCTGCACTTCTTGTTCAAAAATCAGGAAAAGAAAAG  
ATTTGAAGACCCCAAGTCTTGTCAATAACTTGCTGTGTGGAAGCAGCGGGGGAAGACCTA  
GAACCCCTTTCCCCAGCACTTGGTTTTTCCAACATGATATTTATGAGTAATTTATTTTGATA  
TGTACATCTCTTATTTTCTTACATTATTTATGCCCCCAAATTATATTTATGTATGTAAGT  
GAGGTTTGTTTTGTATATTAAATGGAGTTTGT

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**FIGURE 78**

MRSGCVVVHVWILAGLWLAVAGRPLAFSDAGPHVHYGWDPIRLRHLYTSGPHGLSSCFL  
RIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDC  
AFEEEIRPDGYNVYRSEKHLRPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLR  
GHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSF EK

**Signal peptide:**  
amino acids 1-22

**Casein kinase II phosphorylation site:**  
amino acids 78-82, 116-120, 190-194, 204-208

**N-myristoylation site:**  
amino acids 15-21, 54-60, 66-72, 201-207

**Prokaryotic membrane lipoprotein lipid attachment site:**  
amino acids 48-59

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**FIGURE 79**

CGGACGCGTGGGCGGACGCGTGGGCCTGGGCAAGGGCCGGGGCGCCGGGCGGAGCCACCTCTTCCC  
CTCCCCCGCTTCCCTGTGCGCGCTCCGCTGGCTGGACGCGCTGGAGGAGTGGAGCAGCACCCGGCCG  
GCCCTGGGGGCTGACAGTCGGCAAAGTTTGGCCCGAAGAGGAAGTGGTCTCAAACCCCGGCAGGTG  
GCGACCAGGCCAGACCAGGGGCGCTCGTGCCTGCGGGCGGGCTGTAGGCGAGGGCGCGCCCCAGT  
GCCGAGACCCGGGGCTTCAAGAGCCGGCCCCGGGAGAGAAGAGTGC GGCGGCGGACGGAGAAAACA  
ACTCAAAGTTGGCGAAAGGCACCGCCCCCTACTCCCGGGCTGCCGCGCCTCCCCGCCCCCAGCCC  
TGGCATCCAGAGTACGGGTGAGCCCCGGGCCATGGAGCCCCCTGGGGAGGCGGCACCAGGGAGCC  
TGGGCGCCCCGGGGCTCCGCGCGCAGCCCCATCGGGTAGACCACAGAAGCTCCGGGACCCTTCCGGCA  
CCTCTGGACAGCCCAGGATGCTGTTGGCCACCCTCCTCCTCCTCCTTGGAGGCGCTCTGGCCC  
ATCCAGACCCGATTATTTTTCCAAATCATGCTTGTGAGGACCCCCCAGCAGTGCTCTTAGAAGTGC  
AGGGCACCTTACAGAGGCCCTGGTCCGGGACAGCCGCACCTCCCCTGCCAACTGCACCTGGCTCA  
TCCTGGGCAGCAAGGAACAGACTGTACCATCAGGTTCCAGAAGCTACACCTGGCCTGTGGCTCAG  
AGCGCTTAACCTACGCTCCCCTCTCCAGCCACTGATCTCCCTGTGTGAGGCACCTCCCAGCCCTC  
TGCAGCTGCCCCGGGGGCAACGTCAACATCACTTACAGCTATGCTGGGGCCAGAGCACCCATGGGCC  
AGGGCTTCTGCTCTCCTACAGCCAAGATTGGCTGATGTGCCCTGCAGGAAGAGTTTCAGTGCCCTGA  
ACCACCGCTGTGTATCTGCTGTCCAGCGCTGTGATGGGGTTGATGCCCTGTGGCGATGGCTGTGATG  
AAGCAGGTTGCAGCTCAGACCCCTTCCCTGGCCTGACCCCAAGACCCGTCCTCCTCCTGTGCA  
ATGTACCTTGGAGGACTTCTATGGGGTCTTCTCCTCTCCTGGATATACACACCTAGCCTCAGTCT  
CCCACCCCCAGTCTTGCCTTGGCTGCTGGACCCCCATGATGGCCGGCGGCTGGCCGTGCGCTTCA  
CAGCCCTGGACTTGGGCTTTGGAGATGCAGTGCATGTGTATGACGGCCCTGGGCCCCCTGAGAGCT  
CCCGACTACTGCGTAGTCTCACCCACTTCAAGCAATGGCAAGGCTGTCACTGTGGAGACACTGTCTG  
GCCAGGCTGTTGTGTCTTACCACACAGTTGCTTGGAGCAATGGTTCGTGGCTTCAATGCCACCTACC  
ATGTGCGGGGCTATTTGCTTGGCTTGGGACAGACCTGTGGCTTAGGCTCTGGCCTGGGAGCTGGCG  
AAGGCCTAGGTGAGCGCTGCTACAGTGAGGCACAGCGCTGTGACGGCTCATGGGACTGTGCTGACG  
GCACAGATGAGGAGGACTGCCCAGGCTGCCACCTGGACACTTCCCCTGTGGGGCTGCTGGCACCT  
CTGGTGCCACAGCCTGCTACCTGCCTGCTGACCGCTGCAACTACCAGACTTTCTGTGCTGATGGAG  
CAGATGAGAGACGCTGTGCGCATTTGCCAGCCTGGCAATTTCCGATGCCGGGACGAGAAGTGCCTGT  
ATGAGACGTGGCTGTGCGATGGGCAGCCAGACTGTGCGGACGGCAGTGATGAGTGGGACTGCTCCT  
ATGTTCTGCCCCGCAAGGTCATTACAGCTGCAGTCACTTGGCAGCCTAGTGTGCGGCTGCTCCTGG  
TCATCGCCCTGGGCTGCACCTGCAAGCTCTATGCCATTGCAACCCAGGAGTACAGCATCTTTGCC  
CCCTCTCCCGGATGGAGGCTGAGATTGTGACGAGCAGGACGGCACCCCTTCTACGGGACGCTCATTTG  
CCCAGGGTGCCATCCCACCTGTAGAAGACTTTCTACAGAGAATCCTAATGATAACTCAGTGCTGG  
GCAACCTGCGTTCTCTGCTACAGATCTTACGCCAGGATATGACTCCAGGAGGTGGCCAGGTGCC  
GCCGTGCTCAGCGGGGCGCTTGTATGCGACGCCTGGTACGCCGTCTCCGCCGCTGGGGCTTGTCTC  
CTCGAACCAACACCCCGGCTCGGGCCTCTGAGGCCAGATCCAGGTACACCTTCTGCTGCTCCCC  
TTGAGGCCCTAGATGGTGGCACAGGTCCAGCCCGTGAGGGCGGGCAGTGGGTGGGCAAGATGGGG  
AGCAGGCACCCCCACTGCCCATCAAGGCTCCCCTCCCATCTGCTAGCACGTCTCCAGCCCCCACTA  
CTGTCCCTGAAGCCCCAGGGCCACTGCCCTCACTGCCCCCTAGAGCCATCACTATTGTCTGGAGTGG  
TGCAGGCCCTGCGAGGCCGCTGTTGCCCAGCCTGGGGCCCCCAGGACCAACCCGGAGCCCCCCTG  
GACCCACACAGCAGTCTTGGCCCTGGAAGATGAGGACGATGTGCTACTGGTGCCACTGGCTGAGC  
CGGGGGTGTGGGTAGCTGAGGCAGAGGATGAGCCACTGCTTACCTGAGGGGACCTGGGGGCTCTAC  
TGAGGCCTCTCCCCTGGGGGCTCTACTCATAGTGGCACAACCTTTTAGAGGTGGGTGAGCCTCCCC  
TCCACCCTTCTCCTTCCCTGCTCCCTGGATTTCAGGGACTTGGTGGGCCTCCCGTTGACCCTATGTAG  
CTGCTATAAAGTTAAGTGTCCCTCAGGCAGGAGAGGGCTCACAGAGTCTCCTCTGTACGTGGCCA  
TGGCCAGACACCCAGTCCCTTCAACACCACCTGCTCCCCACGCCACCACCATTTGGGTGGCTGTT  
TTTAAAGTAAAGTTCTTAGAGGATCATAGGTCTGGACACTCCATCCTTGCCAAACCTCTACCCA  
AAAGTGGCCTTAAGCACCGGAATGCCAATTAAGTAGAGACCTCCAGCCCCCAAGGGGAGGATTTG  
GGCAGAACCTGAGGTTTTGCCATCCACAATCCCTCCTACAGGGCCTGGCTCACAAAAGAGTGCAA  
CAAATGCTTCTATTCCATAGCTACGGCATTTGCTCAGTAAGTTGAGGTCAAAAATAAGGAATCATA  
CATCTC

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**FIGURE 80**

MLLATLLLLLLGGALAHDPRIIFPNHACEDPPAVLLEVGQTLQRPLVRDSRTSPANCTWL  
ILGSKEQTVTIRFQKLHLACGSERLTLRSPLQPLISLCEAPPSPLQLPGGNVTITYSYAG  
ARAPMGQGFLLSYSQDWLMCLQEEFQCLNHRCVSAVQRCDGVDACGDGSDEAGCSSDPFP  
GLTPRPVPSLPCNVTLEDIFYGVFSSPGYTHLASVSHPOQSWLLDPHDGRRRLAVRFTALD  
LGFGDAVHVYDGPGPPESSRLLRSLTHFSNGKAVTVETLSGQAVVSYHTVAWSNGRGFNA  
TYHVRGYCLPWDRPCGLGSGLGAGEGLGERCYSEAQRCDGSWDCADGTDEEDCPGCPPGH  
FPCGAAGTSGATACYLPADRCNYQTFCADGADERRCRHCQPGNFRRCRDEKCVYETWVCDG  
QPD CADGSDEWDCSYVLPRKVITA AVIGSLVCGLLLVIALGCTCKLYAIRTQEYSIFAPL  
SRMEAEIVQQQAPPSYGQLIAQGAIPPVEDFPTENPNDNSVLGNLRSLLQILRQDMTPGG  
GPGARRRQRGRLMRRLVRRLRRWGLLPRTNTPARASEARSQVTPSAAPLEALDGGTGPAR  
EGGAVGGQDGEQAPPLPIKAPLPSASTSPAPTTVPEAPGPLPSLPLEPSLLSGVVQALRG  
RLLP SLGPPGPTRSPPGPHTAVLALEDEDDVLLVPLAEPGVWVAEAEDEPLLT

**Important features:**

**Signal peptide:**

amino acids 1-16

**Transmembrane domain:**

amino acids 442-462

**LDL-receptor class A (LDLRA) domain proteins:**

amino acids 411-431, 152-171, 331-350 and 374-393

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## FIGURE 81

CTTCTGTGCTGTTCCCTTCTTGCCTCTAACTTGTAACAAGACGTACTAGGACGATGCTAA  
TGGAAAGTCACAAACCGCTGGGTTTTTGAAAGGATCCTTGGGACCTCATGCACATTTGTG  
GAAACTGGATGGAGAGATTTGGGGAAGCATGGACTCTTTAGCCAGCTTAGTTCTCTGTGG  
AGTCAGCTTGCTCCTTTCTGGAAGTGTGGAAGGTGCCATGGACTTGATCTTGATCAATTC  
CCTACCTCTTGTATCTGATGCTGAAACATCTCTCACCTGCATTGCCTCTGGGTGGCGCCC  
CCATGAGCCCATCACCATAGGAAGGGACTTTGAAGCCTTAATGAACCAGCACCAGGATCC  
GCTGGAAGTTACTCAAGATGTGACCAGAGAATGGGCTAAAAAAGTTGTTTGAAGAGAGA  
AAAGGCTAGTAAGATCAATGGTGCTTATTTCTGTGAAGGGCGAGTTCGAGGAGAGGCAAT  
CAGGATACGAACCATGAAGATGCGTCAACAAGCTTCCTTCTACCAGCTACTTTAACTAT  
GACTGTGGACAAGGGAGATAACGTGAACATATCTTTCAAAAAGGTATTGATTAAAGAAGA  
AGATGCAGTGATTTACAAAAATGGTTCCTTCATCCATTGAGTGCCTCCGGCATGAAGTACC  
TGATATTCTAGAAGTACACCTGCCTCATGCTCAGCCCCAGGATGCTGGAGTGTACTCGGC  
CAGGTATATAGGAGGAAACCTCTTCACCTCGGCCTTCACCAGGCTGATAGTCCGGAGATG  
TGAAGCCCAGAAGTGGGGACCTGAATGCAACCATCTCTGTACTGCTTGTATGAACAATGG  
TGTCTGCCATGAAGATACTGGAGAATGCATTTGCCCTCCTGGGTTTATGGGAAGGACGTG  
TGAGAAGGCTTGTGAAGTGCACACGTTTGGCAGAACTTGTAAGAAAGGTGCAGTGGACA  
AGAGGGATGCAAGTCTTATGTGTTCTGTCTCCCTGACCCCTATGGGTGTTCTCTGTGCCAC  
AGGCTGGAAGGGTCTGCAGTGCAATGAAGCATGCCACCCTGGTTTTTACGGGGCCAGATTG  
TAAGCTTAGGTGCAGCTGCAACAATGGGGAGATGTGTGATCGCTTCCAAGGATGTCTCTG  
CTCTCCAGGATGGCAGGGGCTCCAGTGTGAGAGAGAAGGCATACCGAGGATGACCCCAA  
GATAGTGGATTTGCCAGATCATATAGAAGTAAACAGTGGTAAATTTAATCCCATTGTCAA  
AGCTTCTGGCTGGCCGCTACCTACTAATGAAGAAATGACCCTGGTGAAGCCGGATGGGAC  
AGTGCTCCATCCAAAAGACTTTAACCATACGGATCATTTCTCAGTAGCCATATTCACCAT  
CCACCGGATCCTCCCCCTGACTCAGGAGTTTGGGTCTGCAGTGTGAACACAGTGGCTGG  
GATGGTGGAAAAGCCCTTCAACATTTCTGTAAAGTTCTTCCAAAGCCCTGAATGCCCC  
AAACGTGATTGACACTGGACATAACTTTGCTGTGCATCAACATCAGCTCTGAGCCTTACTT  
TGGGGATGGACCAATCAAATCCAAGAAGCTTCTATACAAACCCGTTAATCACTATGAGGC  
TTGGCAACATATTCAAGTGACAAATGAGATTGTTTAACTCAACTATTTGGAACCTCGGAC  
AGAATATGAACTCTGTGTGCAACTGGTCCGTGCTGGAGAGGGTGGGGAAGGGCATCCTGG  
ACCTGTGAGACGCTTCACAACAGCTTCTATCGGACTCCCTCCTCCAAGAGGTCTAAATCT  
CCTGCCTAAAAGTCAGACCACTCTAAATTTGACCTGGCAACCAATATTTCCAAGCTCGGA  
AGATGACTTTTATGTTGAAGTGGAGAGAAGGTCTGTGCAAAAAAGTGATCAGCAGAATAT  
TAAAGTTCAGGCAACTTGACTTCGGTGCTACTTAACAACTTACATCCCAGGGAGCAGTA  
CGTGGTCCGAGCTAGAGTCAACACCAAGGCCAGGGGGAATGGAGTGAAGATCTCACTGC  
TTGGACCCTTAGTGACATTCTTCTCCTCAACCAGAAAACATCAAGATTTCCAACATTAC  
ACACTCCTCGGCTGTGATTTCTTGGACAATATTGGATGGCTATTCTATTTCTTCTATTAC  
TATCCGTTACAAGGTTCAAGGCAAGAATGAAGACCAGCACGTTGATGTGAAGATAAAGAA  
TGCCACCATCATTGAGTATCAGCTCAAGGGCCTAGAGCCTGAAACAGCATACCAGGTGGA  
CATTTTTGCAGAGAAACAATAGGGTCAAGCAACCCAGCCTTTTCTCATGAACTGGTGAC  
CCTCCCAGAATCTCAAGCACCAGCGGACCTCGGAGGGGGGAAGATGCTGCTTATAGCCAT  
CCTTGGCTCTGCTGGAATGACCTGCCTGACTGTGCTGTTGGCCTTTCTGATCATATTGCA  
ATTGAAGAGGGCAAATGTGCAAAGGAGAATGGCCCAAGCCTTCCAAAACGTGAGGGAAGA  
ACCAGCTGTGCAGTTCAACTCAGGGACTCTGGCCCTAAACAGGAAGGTCAAAAACAACCC  
AGATCCTACAATTTATCCAGTGCTTGACTGGAATGACATCAAATTTCAAGATGTGATTGG  
GGAGGGCAATTTTGGCCAAGTTCTTAAGGCGCGCATCAAGAAGGATGGGTTACGGATGGA  
TGCTGCCATCAAAAGAATGAAAGAATATGCCTCCAAAAGATGATCACAGGGACTTTGCAGG  
AGAACTGGAAGTTCTTTGTAACTTGACACCATCCAAACATCATCAATCTCTTAGGAGC

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ATGTGAACATCGAGGCTACTTGTACCTGGCCATTGAGTACGCGCCCCATGGAAACCTTCT  
GGACTTCCTTCGCAAGAGCCGTGTGCTGGAGACGGACCCAGCATTTGCCATTGCCAATAG  
CACCGCGTCCACACTGTCTCCAGCAGCTCCTTCACTTCGCTGCCGACGTGGCCCCGGGG  
CATGGACTACTTGAGCCAAAAACAGTTTATCCACAGGGATCTGGCTGCCAGAAACATTTT  
AGTTGGTGAAAACTATGTGGCAAAAAATAGCAGATTTTGGATTGTCCCGAGGTCAAGAGGT  
GTACGTGAAAAAGACAATGGGAAGGCTCCAGTGCGCTGGATGGCCATCGAGTCACTGAA  
TTACAGTGTGTACACAACCAACAGTGATGTATGGTCCTATGGTGTGTTACTATGGGAGAT  
TGTTAGCTTAGGAGGCACACCCTACTGCGGGATGACTTGTGCAGAACTCTACGAGAAGCT  
GCCCCAGGGCTACAGACTGGAGAAGCCCCTGAACTGTGATGATGAGGTGTATGATCTAAT  
GAGACAATGCTGGCGGGAGAAGCCTTATGAGAGGCCATCATTTGCCCAGATATTGGTGTC  
CTTAAACAGAAATGTTAGAGGAGCGAAAGACCTACGTGAATACCACGCTTTATGAGAAGTT  
TACTTATGCAGGAATTGACTGTTCTGCTGAAGAAGCGGCCTAGGACAGAACATCTGTATA  
CCCTCTGTTTCCCTTTTCACTGGCATGGGAGACCCTTGACAACCTGCTGAGAAAACATGCCT  
CTGCCAAAGGATGTGATATATAAGTGTACATATGTGCTGGAATTCTAACAAGTCATAGGT  
TAATATTTAAGACACTGAAAAATCTAAGTGATATAAATCAGATTCTTCTCTCTCATTTTA  
TCCCTCACCTGTAGCATGCCAGTCCCGTTTTCATTTAGTCATGTGACCACTCTGTCTTG TG  
TTTCCACAGCCTGCAAGTTCAGTCCAGGATGCTAACATCTAAAAATAGACTTAAATCTCA  
TTGCTTACAAGCCTAAGAATCTTTAGAGAAGTATACATAAGTTTAGGATAAAATAATGGG  
ATTTTCTTTTCTTTTCTCTGTAATATTGACTTGTATATTTTAAGAAATAACAGAAAGCC  
TGGGTGACATTTGGGAGACATGTGACATTTATATATTGAATTAATATCCCTACATGTATT  
GCACATTGTAAAAAGTTTTAGTTTTGATGAGTTGTGAGTTTACCTTGTATACTGTAGGCA  
CACTTTGCACTGATATATCATGAGTGAATAAATGTCTTGCCTACTCAAAAAAAAAAAAA

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**FIGURE 82**

MDSLASLVLCGVSLLLSGTVEGAMDLILINSLPLVSDAETSLTCIASGWRPHEPITIGRD  
FEALMNQHQDPLEVTQDVTREWAKKVWVKREKASKINGAYFCEGRVRGEAIRITMKMRQ  
QASFLPATLTMTVDKGDVNISFKKVLIKEEDAVIYKNGSFIHSVPRHEVPDILEVHLPH  
AQPQDAGVYSARYIGGNLFTSAFTRLIVRRCEAQKWGPECNHLCTACMNNGVCHEDTGEC  
ICPPGFMGRTCEKACELHTFGRTCKERCSCGEGCKSYVFCLPDPYGCSCATGWKGLQCNE  
ACHPGFYGPDCKLRCSNNGEMCDRFQGCCLSPGWQGLQCEREGIPRMTPKIVDLPDHIE  
VNSGKFNPICKASGWPLPTNEEMTLVKPDGTVLHPKDFNHTDHFSAIFTIHRILPPDSG  
VWVCSVNTVAGMVEKPFNISVKVLPKPLNAPNVIDTGHNFAVINISSEPYFGDGPIKSKK  
LLYKPVNHYEAWQHIQVTNEIVTLNYLEPRTEYELCVQLVRRGEGGEGHPGPVRRFTTAS  
IGLPPPRGLNLLPKSQTTLNLTWQPIFPSSEDDFYVEVERRSVQKSDQQNIKVPGNLTSV  
LLNNLHPREQYVVRARVNTKAQGEWSEDLTAWTSLSDILPPQPENIKISNITHSSAVISWT  
ILDGYSISSITIRYKVQGKNEDQHVDVKIKNATIIQYQLKGLEPETAYQVDIFAENNIGS  
SNPAFSHELVTLPESQAPADLGGGKMLLIAILGSAGMTCLTVLLAFLIILQLKRANVQRR  
MAQAFQNVREEPVQFNSGTLALNRKVKNPDPPTIYPVLDWNDIKFQDVI GEGNFGQVLK  
ARIKKDGLRMDAAIKRMKEYASKDDHRDFAGELEVLCKLGHPNIIINLLGACEHRGYLYL  
AIEYAPHGNLLDFLRKSRLVLETDPAFAIANSTASTLSSQQLLHFAADVARGMDYLSQKQF  
IHRDLAARNILVGENYVAKIADFGLSRGQEVYVKKTMGRLPVVRWMAIESLNYSVYTTNSD  
VWSYGVLLWEIVSLGGTPYCGMTCAELYEKLPGYRLEKPLNCDDEVYDLMRQCWREKPY  
ERPSFAQILVSLNRMLEERKTYVNTTLYEKFTYAGIDCSAEAAA

**Signal sequence:**

1-38

**Transmembrane domain:**

750-770

**N-glycosylation site:**

140-143, 158-161, 399-402, 438-441, 464-467, 560-563, 596-599, 649-652, 691-694, 930-933, 1011-1014, 1104-1107

**cAMP- and cGMP-dependent protein kinase phosphorylation site:**

534-537

**Tyrosine kinase phosphorylation site:**

149-156, 808-816, 1094-1102

**N-myristoylation site:**

18-23, 98-103, 187-192, 196-201, 270-275, 286-291, 295-300, 420-425, 595-600, 984-989, 1036-1041, 1041-1046, 1115-1120

**Prokaryotic membrane lipoprotein lipid attachment site:**

882-892



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EGF-like domain cysteine pattern signature:  
240-251, 287-298, 329-340

Tyrosine protein kinases specific active-site signature:  
960-972

Protein kinase domain:  
824-1092

Fibronectin type III domain:  
444-529, 543-626, 639-724

EGF-like domain:  
220-251, 268-298

laminin\_EGF Laminin EGF-like (Domains III and V):  
219-268

Immunoglobulin domain:  
156-193

Zinc finger:  
295-313

Receptor tyrosine kinase:  
844-868, 869-898, 936-982, 986-1024, 1025-1052, 1052-1088

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**FIGURE 83**

CGCGCCGGGCGCAGGGAGCTGAGTGGACGGCTCGAGACGGCGGCGCGTGCAGCAGCTCCA  
GAAAGCAGCGAGTTGGCAGAGCAGGGCTGCATTTCCAGCAGGAGCTGCGAGCACAGTGCT  
GGCTCACAACAAGATGCTCAAGGTGTCAGCCGTACTGTGTGTGTGTGCAGCCGCTTGGTG  
CAGTCAGTCTCTCGCAGCTGCCGCGGCGGTGGCTGCAGCCGGGGGGCGGTCCGACGGCGG  
TAATTTTCTGGATGATAACAATGGCTCACCACAATCTCTCAGTATGACAAGGAAGTCGG  
ACAGTGGAAACAAATTCCGAGACGAAGTAGAGGATGATTATTTCCGCACTTGGAGTCCAGG  
AAAACCCCTTCGATCAGGCTTTAGATCCAGCTAAGGATCCATGCTTAAAGATGAAATGTAG  
TCGCCATAAAGTATGCATTGCTCAAGATTCTCAGACTGCAGTCTGCATTAGTCACCGGAG  
GCTTACACACAGGATGAAAGAAGCAGGAGTAGACCATAGGCAGTGGAGGGGTCCCATATT  
ATCCACCTGCAAGCAGTGCCCAAGTGGTCTATCCAGCCCTGTTTGTGGTTTCAGATGGTCA  
TACCTACTCTTTTCAGTGCAAATAAGATATCAGGCATGTGTCTTAGGAAAACAGATCTC  
AGTCAAATGTGAAGGACATTGCCCATGTCTTCAGATAAGCCCACCAGTACAAGCAGAAA  
TGTTAAGAGAGCATGCAGTGACCTGGAGTTCAGGGAAGTGGCAAACAGATTGCGGGACTG  
GTTCAAGGCCCTTCATGAAAGTGGAAGTCAAAACAAGAAGACAAAAACATTGCTGAGGCC  
TGAGAGAAGCAGATTGATACCAAGCATCTTGCCAAATTGCAAGGACTCACTTGGCTGGAT  
GTTTAACAGACTTGATACAACTATGACCTGCTATTGGACCAGTCAGAGCTCAGAAGCAT  
TTACCTTGATAAGAATGAACAGTGTACCAAGGCATTCTTCAATTCTTGTGACACATACAA  
GGACAGTTTAATATCTAATAATGAGTGGTGCTACTGCTTCCAGAGACAGCAAGACCCACC  
TTGCCAGACTGAGCTCAGCAATATTCAGAAGCGGCAAGGGGTAAAGAAGCTCCTAGGACA  
GTATATCCCCCTGTGTGATGAAGATGGTTACTACAAGCCAACACAATGTCATGGCAGTGT  
TGGACAGTGCTGGTGTGTTGACAGATATGGAAATGAAGTCATGGGATCCAGAATAAATGG  
TGTTGCAGATTGTGCTATAGATTTTGAGATCTCCGGAGATTTTGCTAGTGGCGATTTTCA  
TGAATGGACTGATGATGAGGATGATGAAGACGATATTATGAATGATGAAGATGAAATTTGA  
AGATGATGATGAAGATGAAGGGGATGATGATGATGGTGGTGTGATGACCATGATGTATACAT  
TTGATTGATGACAGTTGAAATCAATAAATTCTACATTTCTAATATTTACAAAAATGATAG  
CCTATTTAAATATCTTCTTCCCCAATAACAAAATGATTCTAAACCTCACATATATTTT  
GTATAATTATTTGAAAAATTGCAGCTAAAGTTATAGAACTTTATGTTTAAATAAGAATCA  
TTTGCTTTGAGTTTTTATATTCCTTACACAAAAAGAAAATACATATGCAGTCTAGTCAGA  
CAAAATAAAGTTTTGAAGTGCTACTATAATAAATTTTTTCACGAGAACAACTTTGTAAAT  
CTTCCATAAGCAAAATGACAGCTAGTGCTTGGGATCGTACATGTTAATTTTTTGAAGAT  
AATTCTAAGTGAATTTAAATAAATAAATTTTTAATGACCTGGGTCTTAAGGATTTAGG  
AAAAATATGCATGCTTAAATTGCATTTCCAAAGTAGCATCTTGCTAGACCCTAGATGAGTC  
AGGATAACAGAGAGATACCACATGACTCCAAAAAAAAAAAAAAAAA

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**FIGURE 84**

MLKVSAVLCVCAAAWCSQSLAAAAVAAAGGRSDGGNFLDDKQWLTTISQYDKEVGQWNK  
FRDEVEDDYFRTWSPGKPFQALDPAKDPCLKMKCSRHKVCIAQDSQTAVCISHRRLTHR  
MKEAGVDHRQWRGPILSTCKQCPVVYPSPVCGSDGHTYSFQCKLEYQACVLGKQISVKCE  
GHCPCPSDKPTSTSRNVKRACSDLEFREVANRLRDWFKALHESGSQNKTKTLLRPERSR  
FDTSILPICKDSLGMWFMNRLDTNYDLLLDQSELRSIYLDKNEQCTKAFFNSCDTYKDSLI  
SNNEWCYCFQRQDPPCQTELSNIQKRQGVKKLLGQYIPLCDEDGYKPTQCHGSVGQCW  
CVDRYGNEVMGSRINGVADCAIDFEISGDFASGDFHEWTDDEDDIMNDEDEIEDDE  
DEGDDDDGGDDHDVYI

**Important features:****Signal peptide:**

amino acids 1-16

**Leucine zipper pattern:**

amino acids 246-267

**N-myristoylation sites:**

amino acids 357-362, 371-376 and 376-381

**Thyroglobulin type-1 repeat proteins:**

amino acids 353-365 and 339-352

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**FIGURE 85**

CCCACGCGTCCGGCACTGCAGTCTCCAGCCTGAGCCATGGGCCGCCGAGCCCTCCTGCTC  
CTGCTTCTGTCTTTTCTGGCGCCCTGGGCCACCATAGCCCTCCGGCCGGCCTTAAGGGCC  
CTCGGCAGCCTACACTTGCCAACCAACCCACATCCCTCCCGGCTGTAGCCAAGAACTAT  
TCGGTTCTCTACTTCCAACAGAAGGTTGATCATTTTGGATTTAATACTGTGAAAACTTT  
AATCAGCGGTACCTAGTAGCTGATAAATACTGGAAGAAAAATGGTGGATCAATACTTTTC  
TACACTGGTAATGAAGGGGACATTATCTGGTTTTGTAAATAACACGGGGTTCATGTGGGAT  
GTGGCTGAGGAACTGAAAGCTATGTTGGTGTGCTGAACATCGATACTATGGAGAGTCT  
CTCCCCTTTGGTGACAACCTCATTCAAGGATTCCAGACACTTGAATTCCTGACATCAGAA  
CAAGCTCTGGCTGATTTTGCAGAGTTAATCAAACACTTGAAAAGAACAATCCCAGGAGCT  
GAAAATCAACCTGTCAATGCCATAGGAGGCTCCTATGGTGGCATGCTTGCCGCTGGTTT  
AGGATGAAATATCCTCATATGGTAGTTGGAGCTCTTGACAGCTTCTGCCCCTATCTGGCAG  
TTTGAGGATTTAGTACCTTGTGGTGTATTTATGAAGATCGTAACTACAGATTTTAGGAAA  
AGCGGTCCACATTGTTTCAGAGAGCATCCACAGGTCCTGGGATGCCATTAATCGACTCTCA  
AATACTGGCAGTGGTTTTGCAGTGGCTTACTGGAGCCCTTCACTTATGCAGCCCATTA  
TCTCAGGACATCCAACATTTGAAAGACTGGATCTCTGAAACCTGGGTGAATCTGGCAATG  
GTGGACTATCCTTATGCCTCTAACTTTTTACAGCCTTTGCCTGCTTGGCCTATCAAGGTA  
GTGTGCCAGTATTTGAAAAATCCCAATGTATCTGATTCACTGCTGCTGCAGAATATTTTC  
CAAGCTCTGAATGTATATTACAATTATTCGGGCCAGGTGAAATGCCTGAATATTTTCAGAG  
ACAGCAACTAGCAGTCTGGGAACACTGGGTTGGAGCTATCAGGCCTGCACAGAAGTAGTC  
ATGCCCTTTTGTACTAATGGTGTGATGACATGTTTGAACCTCACTCATGGAACTTAAAG  
GAACTTTCTGATGACTGTTTTCAACAGTGGGGTGTGAGACCAAGGCCCTCCTGGATCACT  
ACTATGTATGGAGGCCAAAACATTAGTTTACACACAAACATTTGTTTTTCAAGCAATGGTGAA  
CTAGACCCCTGGTCAGGAGGTGGAGTAACTAAGGATATCACAGACACTCTGGTTGCAGTC  
ACCATCTCAGAGGGGGCCCACTTAGATCTCCGCACCAAGAATGCCTTGGATCCTATG  
TCTGTGCTGTTAGCCCGCTCCTTGGAAGTTAGACATATGAAGAATTGGATCAGAGATTTTC  
TATGACAGTGCGGGAAAGCAGCACTGAGAACTTTTGATTGTTTTCAATTTCTTCTTTTA  
TGTTTACACCACCACATTCCCATTCACTTTGATTTTCTACATGTAATTACCTTCTTTTGT  
TTATCATTAGATTTGATGGGGCCAAAGTTGAGATAGAATAGAGGGTGATGACGGTAAGAG  
CAAGTGTCCCATGAATGTGATTTCTTGGGTTCTCACTGTCCTTTGCACCACGTCTAGGAA  
GAATCTTCTTGATAGCTCTCCACACCATCAGTGGCCCTCATAACTGGAGTAGAGTTCTCT  
GGTTGCTTTTCATAAGAGGGAGAGTTACTTTC

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**FIGURE 86**

MGRRALLLLLLSFLAPWATIALR'PALRALGSLHLPTNPTSLPAVAKNYSVLYFQQKVDHF  
GFNTVKTFFNQRYLVADKYWKKNNGSILFYTGNEGDI IWFCNNTGFMWDVAEELKAMLVFA  
EHRYYGESLPFGDNSFKDSRHLNFLTSEQALADFAELIKHLKRTIPGAENQPVIAIGGSY  
GGMLAAWFRMKYPHMMVVGALAASAPIWQFEDLVPCGVFMKIVTTDFRKSGPHCSESIHRS  
WDAINRLSNTGSGLQWLTGALHLCSP LTSQDIQHLKDWISETWVNLAMVDYPYASNFLQP  
LPAWPIKVVVCQYLKNPNVSDSLLLQNI FQALNVYYNYSQGVKCLNISETATSSLGTLGWS  
YQACTEVVMPFCTNGVDDMFEPHSWNLKELSDDCFQQWGVRRPRPSWITMYGGKNISSHT  
NIVFSNGELDPWSGGGVTKDITDTLVAVTISEGAHHLDLRTKNALDPMSVLLARSLEVRH  
MKNWIRDFYDSAGKQH

**Signal sequence:**

1-18

**Transmembrane domain:**

None

**N-glycosylation site:**

47-50, 101-104, 317-320, 336-339, 345-348, 415-418

**Glycosaminoglycan attachment site:**

433-436

**N-myristoylation site:**

178-183, 181-186, 182-187, 198-203, 339-344, 434-439

**Amidation site:**

1-4

**alpha/beta hydrolase fold:**

115-372

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**FIGURE 87**

GGCGGCGTCCGTGAGGGGCTCCTTTGGGCAGGGGTAGTGTTTGGTGTCCCTGTCTTGCGT  
GATATTGACAACTGAAGCTTTCCTGCACCACTGGACTTAAGGAAGAGTGTA CT CGTAGG  
CGGACAGCTTTAGTGGCCGGCCGGCCGCTCTCATCCCCGTAAGGAGCAGAGTCCTTTGT  
ACTGACCAAGATGAGCAACATCTACATCCAGGAGCCTCCCACGAATGGGAAGGTTTTATT  
GAAACTACAGCTGGAGATATTGACATAGAGTTGTGGTCCAAAGAAGCTCCTAAAGCTTG  
CAGAAATTTTATCCAACCTTTGTTTGGAGCTTATTATGACAATACCATTTTTCATAGAGT  
TGTGCCTGGTTTCATAGTCCAAGGCGGAGATCCTACTGGCACAGGGAGTGGTGGAGAGTC  
TATCTATGGAGCGCCATTCAAAGATGAATTTCATTCACGGTTGCGTTTTAATCGGAGAGG  
ACTGGTTGCCATGGCAAATGCTGGTTCATGATAATGGCAGCCAGTTTTTCTTCACACT  
GGGTGAGCAGATGAACTTAACAATAAGCATAACCATCTTTGGAAAGGTTACAGGGGATAC  
AGTATATAACATGTTGCGACTGTCAGAAGTAGACATTGATGATGACGAAAGACCACATAA  
TCCACACAAAATAAAAAGCTGTGAGGTTTTGTTAATCCTTTTGATGACATCATTCCAAG  
GGAAATTAAAAGGCTGAAAAAAGAGAAACCAGAGGAGGAAGTAAAGAAATTGAAACCCAA  
AGGCACAAAAAATTTTAGTTTACTTTTCAATTTGGAGAGGAAGCTGAGGAAGAAGAGGAGGA  
AGTAAATCGAGTTAGTCAGAGCATGAAGGGCAAAAGCAAAAGTAGTCATGACTTGCTTAA  
GGATGATCCACATCTCAGTTCGTTCAGTTGTAGAAAGTGAAAAAGGTGATGCACCAGA  
TTTAGTTGATGATGGAGAAGATGAAAGTGCAGAGCATGATGAATATATTGATGGTGATGA  
AAAGAACCTGATGAGAGAAAGAATTGCCAAAAAATTA AAAAAGGACACAAGTGCGAATGT  
TAAATCAGCTGGAGAAGGAGAAGTGGAGAAGAAATCAGTCAGCCGCAAGTGAAGAGCTCAG  
AAAAGAAGCAAGACAATTAAAACGGGAACCTCTTAGCAGCAAAACAAAAAAGTAGAAAA  
TGCAGCAAAACAAGCAGAAAAAAGAAGTGAAGAGGAAGAAGCCCCCTCCAGATGGTGCTGT  
TGCCGAATACAGAAGAGAAAAAGCAAAAGTATGAAGCTTTGAGGAAGCAACAGTCAAAGAA  
GGGAACCTCCCGGGAAGATCAGACCCTTGCACTGCTGAACCAGTTTAAATCTAAACTCAC  
TCAAGCAATTGCTGAAACACCTGAAAATGACATTCCTGAAACAGAAGTAGAAGATGATGA  
AGGATGGATGTCACATGTACTTCAGTTTGAGGATAAAAGCAGAAAAGTGAAAGATGCAAG  
CATGCAAGACTCAGATACATTTGAAATCTATGATCCTCGGAATCCAGTGAATAAAAGAAG  
GAGGGAAGAAAGCAAAAAGCTGATGAGAGAGAAAAAAGAAAGAAGATAAAATGAGAAATAA  
TGATAACCAGAACTTGCTGGAAATGTGCCTACAATGGCCTTGTAACAGCCATTGTTCCCA  
ACAGCATCACTTAGGGGTGTGAAAAGAAGTATTTTTGAACCTGTTGTCTGGTTTTGAAAA  
ACAATTATCTTGTTTTGCAAATTGTGGAATGATGTAAGCAAAATGCTTTTGGTTACTGGTA  
CATGTGTTTTTTCCTAGCTGACCTTTTATATTGCTAAATCTGAAATAAAATAACTTTCCT  
TCCACAAAAA AAAAAAAAAAAAAAAAAAAAAAAAAA

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**FIGURE 88**

MSNIYIQEPPTNGKVLLKTTAGDIDIELWSKEAPKACRNFIQLCLEAYYDNTIFHRVVPG  
FIVQGGDPTGTGSGGESIYGAPFKDEFHSRLRFNRRGLVAMANAGSHDNGSQFFFTLGRA  
DELNNKHTIFGKVTGDTVYNMLRLSEVDIDDDERPHNPHKIKSCEVLFPFDDIIPREIK  
RLKKEKPEEEVKKLKPKGTKNFSLLSFGEEAEVEEVNRVSQSMKGKSKSSHDLKDDP  
HLSSVPVVESEKGDAPDLVDDGEDESAEHDEYIDGDEKNLMRERIAKKLKKDTSANVKS  
A  
GEGEVEKKSVSRSEELRKEARQLKRELLAAKQKKVENAAKQAEKRSEEEAAPPDGAVAEY  
RREKQKYEALRKQOSKKGTSREDQTLALLNQFKSKLTQAIAETPENDIPETEVEDDEGWM  
SHVLQFEDKSRKVKDASMQSDTFEYDPRNPFVNKRREESKMLMREKKERR

**Important features:****Signal peptide:**

amino acids 1-21

**N-glycosylation sites:**

amino acids 109-112 and 201-204

**Cyclophilin-type peptidyl-prolyl cis-trans isomerase****signature:**

amino acids 49-66

**Homologous region to Cyclophilin-type peptidyl-prolyl cis-trans isomerase:**

amino acids 96-140, 49-89 and 22-51

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**FIGURE 89**

CCCGGCTCCGCTCCCTCTGCCCCCTCGGGGTCGCGCGCCCACGATGCTGCAGGGCCCTGG  
CTCGCTGCTGCTGCTCTTCCTCGCCTCGCACTGCTGCCTGGGCTCGGCGCGCGGGCTCTT  
CCTCTTTGGCCAGCCCGACTTCTCCTACAAGCGCAGCAATTGCAAGCCCATCCCGGTCAA  
CCTGCAGCTGTGCCACGGCATCGAATACCAGAACATGCGGCTGCCCAACCTGCTGGGCCA  
CGAGACCATGAAGGAGGTGCTGGAGCAGGCCGGCGCTTGGATCCCGCTGGTCATGAAGCA  
GTGCCACCCGGACACCAAGAAGTTCTGTGCTCGCTCTTCGCCCCCGTCTGCCTCGATGA  
CCTAGACGAGACCATCCAGCCATGCCACTCGCTCTGCGTGCAGGTGAAGGACCGCTGCGC  
CCCGGTCTGTCCGCCTTCGGCTTCCCCTGGCCCCGACATGCTTGAGTGCGACCGTTTCCC  
CCAGGACAACGACCTTTGCATCCCCCTCGCTAGCAGCGACCACCTCCTGCCAGCCACCGA  
GGAAGCTCCAAAGGTATGTGAAGCCTGCAAAAATAAAAATGATGATGACAACGACATAAT  
GGAAACGCTTTGTAAAAATGATTTTGCCTGAAAATAAAAGTGAAGGAGATAACCTACAT  
CAACCGAGATACCAAAATCATCCTGGAGACCAAGAGCAAGACCATTTACAAGCTGAACGG  
TGTGTCCGAAAGGGACCTGAAGAAATCGGTGCTGTGGCTCAAAGACAGCTTGAGTGCAC  
CTGTGAGGAGATGAACGACATCAACGCGCCCTATCTGGTCAATGGGACAGAAACAGGGTGG  
GGAGCTGGTGATCACCTCGGTGAAGCGGTGGCAGAAGGGGCAGAGAGAGTTCAAGCGCAT  
CTCCCGCAGCATCCGCAAGCTGCAGTGCTAGTCCCGGCATCCTGATGGCTCCGACAGGCC  
TGCTCCAGAGCACGGCTGACCATTTCTGCTCCGGGATCTCAGCTCCCGTTCCCCAAGCAC  
ACTCCTAGCTGCTCCAGTCTCAGCCTGGGCAGCTTCCCCCTGCCTTTTGCACGTTTGCAT  
CCCCAGCATTTCTGAGTTATAAGGCCACAGGAGTGGATAGCTGTTTTACCTAAAGGAA  
AAGCCCACCCGAATCTTGTAGAAATATTCAAACATAAAATCATGAATATTTTAA



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**FIGURE 90**

MLQGPGSLLLLFLASHCCLGSARGLFLFGQPDFSYKRSNCKPIPVNLQLCHGIEYQNMRL  
PNLLGHETMKEVLEQAGAWIPLVMKQCHPDTKKFLCSLFAPVCLDDLDLDETIQCHSLCVQ  
VKDRCAPVMSAFGFPWPDMLECDRFPQDNDLCIPLASSDHLLPATEEAPKVCEACKNKND  
DDNDIMETLCKNDFALKIKVKEITYINRDTKIILETKSKTIYKLVGVSEKDLKKSVLWLK  
DSLQCTCEEMNDINAPYLVMGQKQGELVITSVKRWQKGQREFKRISRSIRKLQC

**Important features:**

**Signal peptide:**

amino acids 1-20

**Cysteine rich domain, homologous to frizzled N terminus:**

amino acids 6-153

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**FIGURE 91**

GGAAGGGGAGGAGCAGGCCACACAGGCACAGGCCGGTGAGGGACCTGCCCAGACCTGGAG  
GGTCTCGCTCTGTCAACAGGCTGGAGTGCAGTGGTGTGATCTTGGCTCATCGTAACCTC  
CACCTCCCGGGTTCAAGTGATTCTCATGCCTCAGCCTCCCGAGTAGCTGGGATTACAGGT  
GGTGACTTCCAAGAGTGACTCCGTCCGAGGAAAATGACTCCCCAGTCGCTGCTGCAGACG  
ACACTGTTCTTGCTGAGTCTGCTCTTCTGGTCCAAGGTGCCACGGCAGGGGCCACAGG  
GAAGACTTTCGCTTCTGCAGCCAGCGGAACCAGACACACAGGAGCAGCCTCCACTACAAA  
CCCACACCAGACCTGCGCATCTCCATCGAGAACTCCGAAGAGGCCCTCACAGTCCATGCC  
CCTTTCCTGTCAGCCACCCTGCTTCCCGATCCTTCCCTGACCCCAGGGGCCTCTACCAC  
TTCTGCCTCTACTGGAACCGACATGCTGGGAGATTACATCTTCTCTATGGCAAGCGTGAC  
TTCTTGCTGAGTGACAAAGCCTCTAGCCTCCTCTGCTTCCAGCACCAGGAGGAGAGCCTG  
GCTCAGGGCCCCCGCTGTTAGCCACTTCTGTACCTCCTGGTGGAGCCCTCAGAACATC  
AGCCTGCCCAGTGCCGCCAGCTTACCTTCTCCTTCCACAGTCCTCCCCACACGGCCGCT  
CACAATGCCTCGGTGGACATGTGCGAGCTCAAAGGGACCTCCAGCTGCTCAGCCAGTTC  
CTGAAGCATCCCCAGAAGGCCTCAAGGAGGCCCTCGGCTGCCCCCGCCAGCCAGCAGTTG  
CAGAGCCTGGAGTCGAAACTGACCTCTGTGAGATTATGGGGGACATGGTGTCTTCGAG  
GAGGACCGGATCAACGCCACGGTGTGGAAGCTCCAGCCCACAGCCGGCCTCCAGGACCTG  
CACATCCACTCCCGGCAGGAGGAGGAGCAGAGCGAGATCATGGAGTACTCGGTGCTGCTG  
CCTCGAACACTCTTCCAGAGGACGAAAGGCCGGAGCGGGGAGGCTGAGAAGAGACTCCTC  
CTGGTGGACTTCAGCAGCCAAGCCCTGTTCCAGGACAAGAAATTCAGCCAAGTCTTGGGT  
GAGAAGGTCTTGGGGATTGTGGTACAGAACACCAAAGTAGCCAACCTCACGGAGCCCGTG  
GTGCTCACTTTCAGCACCAGCTACAGCCGAAGATGTGACTCTGCAATGTGTGTTCTGG  
GTTGAAGACCCACATTGAGCAGCCCGGGCATTGGAGCAGTGTGGGTGTGAGACCGTC  
AGGAGAGAAACCCAAACATCCTGCTTCTGCAACCACTTGACCTACTTTGCAGTGCTGATG  
GTCTCCTCGGTGGAGGTGGACGCCGTGCACAAGCACTACCTGAGCCTCCTCTCTACGTG  
GGCTGTGTCGTCTCTGCCCTGGCCTGCCTTGTCAACATTGCCGCCTACCTCTGCTCCAGG  
GTGCCCCTGCCGTGCAGGAGGAAACCTCGGGACTACACCATCAAGGTGCACATGAACCTG  
CTGCTGGCCGTCTTCTGCTGGACACGAGCTTCTGCTCAGCGAGCCGGTGGCCCTGACA  
GGCTCTGAGGCTGGCTGCCGAGCCAGTGCCATCTTCTGCACTTCTCCCTGCTCACCTGC  
CTTTCCTGGATGGGCCTCGAGGGGTACAACCTCTACCGACTCGTGGTGGAGGTCTTGGC  
ACCTATGTCCCTGGCTACCTACTCAAGCTGAGCGCCATGGGCTGGGGCTTCCCCATCTTT  
CTGGTGACGCTGGTGGCCCTGGTGGATGTGGACAACATATGGCCCCATCATCTTGGCTGTG  
CATAGGACTCCAGAGGGCGTCATCTACCCTTCCATGTGCTGGATCCGGGACTCCCTGGTC  
AGCTACATCACCAACCTGGGCCTCTTCAGCCTGGTGTCTTCTGTTCAACATGGCCATGCTA  
GCCACCATGGTGGTGCAGATCCTGCGGCTGCGCCCCCACACCCAAAAGTGGTCACATGTG  
CTGACACTGCTGGGCCTCAGCCTGGTCTTGGCCTGCCCTGGGCCTTGATCTTCTTCTCC  
TTTGCTTCTGGCACCTTCCAGCTTGTCTGCTCTACCTTTTCAGCATCATCACCTCCTTC  
CAAGGCTTCTCATCTTCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCT  
TCCCCCTGAAGAGCAACTCAGACAGCGCCAGGCTCCCCATCAGCTCGGGCAGCACCTCG  
TCCAGCCGCATCTAGGCCTCCAGCCCACCTGCCCATGTGATGAAGCAGAGATGCGGCCTC  
GTGCGCACTGCCTGTGGCCCCCGAGCCAGGCCAGCCCCAGGCCAGTCAGCCGCAGACT  
TTGGAAAGCCCAACGACCATGGAGAGATGGGCCGTTGCCATGGTGGACGGACTCCCGGGC  
TGGGCTTTTGAATTGGCCTTGGGGACTACTCGGCTCTCACTCAGCTCCCACGGGACTCAG  
AAGTGCGCCGCCATGCTGCCTAGGGTACTGTCCCCACATCTGTCCCAACCCAGCTGGAGG  
CCTGGTCTCTCTTACAACCCCTGGGCCAGCCCTCATTGCTGGGGGCCAGGCCTTGGAT  
CTTGAGGGTCTGGCACATCCTTAATCCTGTGCCCTGCCTGGGACAGAAATGTGGCTCCA  
GTTGCTCTGTCTCTCGTGGTCACCCCTGAGGGCACTCTGCATCCTCTGTCATTTTAACCTC  
AGGTGGCACCCAGGGCGAATGGGGCCAGGGCAGACCTTCAGGGCCAGAGCCCTGGCGGA



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**FIGURE 92**

MT PQSLLQTTLFLLSLLFLVQGAHGRGHREDFR FCSQRNQTHRSSLHYKPTPDLRISIEN  
SEEALTVHAPFPAAHPASRSFPDPRGLYHFCLYWNRHAGRLHLLYGKRD FLLSDKASSLL  
CFQHQEESLAQGPPLLATSVTSWWSPQNISLPSAASF TFSFHSPPHTAAHNASVDMCELK  
RDLQLLSQFLKHPQKASRRPSAAPASQQLOSLESKLT SVRFMGDMVSFEEDRINATVWKL  
QPTAGLQDLHIHSRQEEEQSEIMEYSVLLPRTL FQRTKGRSGEAEKRLLLVDFSSQALFQ  
DKNSSQVLGEKVLGIVVQNTKVANLTEPVVLT FQHQLQPKNVTLQCVFWVEDPTLSSPGH  
WSSAGCETVRRETQTSCFCNHLTYFAVLMVSSVEVD AVHKHYLSLLSYVGCVV SALACLV  
TIAAYLCSRVP LPCR KPRDYTIKVHMNLLLAVFL LDTSFLLSEPVALTGSEAGCRASAI  
FLHFSLLTCLSWMGLEGYNLYRLVVEVFGTYVPGYLLKLSAMGWGFPIFLVTLVALVDVD  
NYGPIILAVHRTPEGVIYPSMCWIRDSLVS YITNLGLFSLVFLFNMAMLATMVVQILRLR  
PHTQKWSHVLTLGLSLVLGLPWALIFFSFASGTFQLVVL YLFSIITSFQGF LIFIWYWS  
MRLQARGGPSPLKSNSDSARLPISSGSTSSSRI

**Important features:****Signal peptide:**

amino acids 1-25

**Putative transmembrane domains:**amino acids 382-398, 402-420, 445-468, 473-491, 519-537,  
568-590 and 634-657**Microbodies C-terminal targeting signal:**

amino acids 691-693

**cAMP- and cGMP-dependent protein kinase phosphorylation sites:**

amino acids 198-201 and 370-373

**N-glycosylation sites:**amino acids 39-42, 148-151, 171-174, 234-237, 303-306, 324-  
327 and 341-344**G-protein coupled receptors family 2 proteins:**

amino acids 475-504

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**FIGURE 93**

CCCACGCGTCCGAAGGCAGACAAAGGTTCAATTTGTAAAGAAGCTCCTTCCAGCACCTCCT  
CTCTTCTCCTTTTGCCCAAACCTCACCCAGTGAGTGTGAGCATTTAAGAAGCATCCTCTGC  
CAAGACCAAAGGAAAGAAGAAAAAGGGCCAAAAGCCAAAATGAAACTGATGGTACTTGT  
TTTCACCATTTGGGCTAACTTTGCTGCTAGGAGTTCAAGCCATGCCTGCAAATCGCCTCTC  
TTGCTACAGAAAGATACTAAAAGATCACAACCTGTCACAACCTTCCGGAAGGAGTAGCTGA  
CCTGACACAGATTGATGTCAATGTCCAGGATCATTTCTGGGATGGGAAGGGATGTGAGAT  
GATCTGTTACTGCAACTTCAGCGAATTGCTCTGCTGCCCAAAGACGTTTTCTTTGGACC  
AAAGATCTCTTTCGTGATTCCTTGCAACAATCAATGAGAATCTTCATGTATTCTGGAGAA  
CACCATTCTGATTTCCCAAACTGCACCTACATCAGTATAACTGCATTTCTAGTTTCTA  
TATAGTGCAATAGAGCATAGATTCTATAAATTCTTACTTGTCTAAGACAAGTAAATCTGT  
GTTAAACAAGTAGTAATAAAAGTTAATTCAATCTAAAAAAAAAAAAA

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## FIGURE 94

MKLMVLVFTIGLTLLLG VQAMPANRLSCYRKILKDNCHNLPEGVADLTQIDVNVQDHFWDGKGCEMICYCNFSELLCCPKDVFFGPKISFVIPCNNQ

**Important features:**

**Signal peptide:**

amino acids 1-20

**N-glycosylation site:**

amino acids 72-76

**Tyrosine kinase phosphorylation site:**

amino acids 63-71

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**FIGURE 95**

GAATTCGGGGCCCCAGGATGCCAACTTTGAATAGGATGAAGACTACAACCTTGTTCCCTTC  
TCATCTGCATCTCCCTGCTCCAGCTGATGGTCCCAGTGAATACTGATGAGACCATAGAGA  
TTATCGTGGAGAATAAGGTCAAGGAACCTTCTTGCCAATCCAGCTAACTATCCCTCCACTG  
TAACGAAGACTCTCTCTTGCACTAGTGTCAAGACTATGAACAGATGGGCCTCCTGCCCTG  
CTGGGATGACTGCTACTGGGTGTGCTTGTGGCTTTGCCTGTGGATCTTGGGAGATCCAGA  
GTGGAGATACTTGCAACTGCCTGTGCTTACTCGTTGACTGGACCACTGCCCCGCTGCTGCC  
AACTGTCCTAAGAATGAAGAGGTGGAGAACCCAGCTTTGATATGATGAATCTAACAAAA  
CTGCAGTCTCAATTTGGAAATCTGACTCATGTGCCTTTAAATGTGTTTCATATTGCCCAT  
TACCCTGCTTCTTGAAATGCTTCTTGAAAAATAAAGACAAATTTGCATGTG

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## FIGURE 96

MKTTTCSLLICISLLQLMVPVNTDEIEIIVENKVKELLANPANYPSTVTKTLSCTSVK  
TMNRWASCPAGMTATGCACGFACGSWEIQSGDTCNCLCLLDWTTARCCQLS



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**FIGURE 97**

GAGGCAGAAAGGCAGAAAGGAGAAAATTTCAGGATAACTCTCCTGAGGGGTGAGCCAAGCC  
CTGCCATGTAGTGACGCAGGACATCAACAAACACAGATAACAGGAAATGATCCATTCCC  
TGTGGTCACTTATTCTAAAGGCCCCAACCTTCAAAGTTCAAGTAGTGATATGGATGACTC  
CACAGAAAGGGAGCAGTCACGCCTTACTTCTTGCCCTTAAGAAAAGAGAAGAAATGAAACT  
GAAGGAGTGTGTTTCCATCCTCCCACGGAAGGAAAGCCCCCTCTGTCCGATCCTCCAAAGA  
CGGAAAGCTGCTGGCTGCAACCTTGCTGCTGGCACTGCTGTCTTGCTGCCTCACGGTGGT  
GTCTTCTTACCAGGTGGCCGCCCTGCAAGGGGACCTGGCCAGCCTCCGGGCAGAGCTGCA  
GGGCCACCACGCGGAGAAGCTGCCAGCAGGAGCAGGAGCCCCAAGGCCGGCCTGGAGGA  
AGCTCCAGCTGTCAACGCGGACTGAAAATCTTTGAACCACCAGCTCCAGGAGAAGGCAA  
CTCCAGTCAGAACAGCAGAAATAAGCGTGCCGTTTCAAGGTCCAGAAGAAACAGTCACTCA  
AGACTGCTTGCAACTGATTGCAGACAGTGAAACACCAACTATACAAAAGGATCTTACAC  
ATTTGTTCCATGGCTTCTCAGCTTTAAAAGGGGAAGTGCCCTAGAAGAAAAAGAGAATAA  
AATATTGGTCAAAGAACTGGTTACTTTTTTATATATGGTCAGGTTTTATATACTGATAA  
GACCTACGCCATGGGACATCTAATTCAGAGGAAGAAGGTCCATGTCTTTGGGGATGAATT  
GAGTCTGGTGACTTTGTTTCGATGTATTCAAATATGCCTGAAACACTACCCAATAATTC  
CTGCTATTGAGCTGGCATTGCAAACTGGAAGAAGGAGATGAACTCCAATTGCAATACC  
AAGAGAAAATGCACAAATATCACTGGATGGAGATGTCACATTTTTTGGTGATTGAACT  
GCTGTGACCTACTTACACCATGTCTGTAGCTATTTTCTCCTCCCTTTCTCTGTACCTCTAAG  
AAGAAAGAATCTAACTGAAAATACCAAAAAAAAAAAAAAAAAA

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**FIGURE 98**

MDDSTEREQSRLTSCCLKREEMKLKECVSILPRKESPSVRSSKDGKLLAATLLLALLSCC  
LTVVSFYQVAALQGD LASLRAELQGHAEKLPAGAGAPKAGLEEAPAVTAGLKIFEPPAP  
GEGNSSQNSRNKRAVQGPETVTQDCLQLIADSETPTIQKGSYTFVPWLLSFKRGSAL EE  
KENKILVKETGYFFIYGQVLYTDKTYAMGHLIQRKKVHVFGDELSLVTLFRCIQNMPETL  
PNNSCYSAGIAKLEEGDELQLAIPRENAQISLDGDVTFFGALKLL

**Transmembrane domain:**

amino acids 47-72

**N-glycosylation site:**

amino acids 124-127, 242-245

**cAMP- and cGMP-dependent protein kinase phosphorylation  
site:**

amino acids 33-36, 173-176

**N-myristoylation site:**

amino acids 96-101

**TNF family proteins:**

amino acids 172-206

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**FIGURE 99**

GCGAGGTGGCGATCGCTGAGAGGCAGGAGGGCCGAGGCGGGCCTGGGAGGCGGCCCCGGAG  
GTGGGGCGCCGCTGGGGCCGGCCCCGCACGGGCTTCATCTGAGGGCGCACGGCCCCGCGACC  
GAGCGTGCGGACTGGCCTCCCAAGCGTGGGGCGACAAGCTGCCGGAGCTGCAATGGGGCCG  
CGGCTGGGGATTCTTGTTTGGCCTCCTGGGCGCCGTGTGGCTGCTCAGCTCGGGCCACGG  
AGAGGAGCAGCCCCCGAGACAGCGGCACAGAGGTGCTTCTGCCAGGTTAGTGGTTACTT  
GGATGATTGTACCTGTGATGTTGAAACCATTGATAGATTTAATAACTACAGGCTTTTCCC  
AAGACTACAAAACTTCTTGAAAGTGACTACTTTAGGTATTACAAGGTAAACCTGAAGAG  
GCCGTGTCCTTTCTGGAATGACATCAGCCAGTGTGGAAGAAGGGACTGTGCTGTCAAACC  
ATGTCAATCTGATGAAGTTCCTGATGGAATTAATCTGCGAGCTACAAGTATTCTGAAGA  
AGCCAATAATCTCATTGAAGAATGTGAACAAGCTGAACGACTTGGAGCAGTGGATGAATC  
TCTGAGTGAGGAAACACAGAAGGCTGTTCTTCAGTGGACCAAGCATGATGATTCTTCAGA  
TAACTTCTGTGAAGCTGATGACATTCACTCCCCTGAAGCTGAATATGTAGATTTGCTTCT  
TAATCCTGAGCGCTACACTGGTTACAAGGGACCAGATGCTTGGAAAATATGGAATGTCAT  
CTACGAAGAAAACCTGTTTAAAGCCACAGACAATTAAGACCTTTAAATCCTTTGGCTTC  
TGGTCAAGGGACAAGTGAAGAGAACACTTTTTACAGTTGGCTAGAAGGTCTCTGTGTAGA  
AAAAAGAGCATTCTACAGACTTATATCTGGCCTACATGCAAGCATTAAATGTGCATTTGAG  
TGCAAGATATCTTTTACAAGAGACCTGGTTAGAAAAGAAATGGGGACACAACATTACAGA  
ATTTCAACAGCGATTTGATGGAATTTTGACTGAAGGAGAAGGTCCAAGAAGGCTTAAGAA  
CTTGATTTTTCTCTACTTAATAGAACTAAGGGCTTTATCCAAAGTGTTACCATTCTTCGA  
GCGCCAGATTTTCAACTCTTTACTGGAAATAAAATTCAGGATGAGGAAAACAAAATGTT  
ACTTCTGGAAATACTTCATGAAATCAAGTCATTTCCCTTTGCATTTTGTGATGAGAATTCATT  
TTTTGCTGGGGATAAAAAAGAAGCACACAACTAAAGGAGGACTTTTCGACTGCATTTTAG  
AAATATTTCAAGAATTATGGATTGTGTTGGTTGTTTTAAATGTCGTCTGTGGGGAAAGCT  
TCAGACTCAGGGTTTGGGCACCTGCTCTGAAGATCTTATTTTCTGAGAAATTGATAGCAA  
TATGCCAGAAAGTGGACCTAGTTATGAATTCCATCTAACCAGACAAGAAATAGTATCATT  
ATTCAACGCATTTGGAAGAATTTCTACAAGTGTGAAAGAATTAGAAAACCTCAGGAACTT  
GTTACAGAATATTCATTAAAGAAAACAAGCTGATATGTGCCTGTTTCTGGACAATGGAGG  
CGAAAGAGTGGAAATTTTCAATCAAAGGCATAATAGCAATGACAGTCTTAAGCCAAACATTT  
TATATAAAGTTGCTTTTGTAAAGGAGAAATTATATTGTTTTAAGTAAACACATTTTAAAA  
ATTGTGTTAAGTCTATGTATAATACTACTGTGAGTAAAAGTAATACTTTAATAATGTGGT  
ACAAATTTTAAAGTTTAAATATTGAATAAAAGGAGGATTATCAAATTAATAAAAAAAAAA  
AAAAAAAAAAAAAAAAAAAAAAAAA

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**FIGURE 100**

MGRGWGFLFGLLGAVWLLSSGHGEEQPPETAARCFQVSGYLDDCTCDVETIDRFNNYR  
LFPRLQKLLESDYFRYYKVNLRPCPFWNDISQCGRRDCAVKPCQSDEVPDGIKSASYKY  
SEANNLIEECEQAERLGAVDESLSEETQKAVLOWTKHDDSSDNFCEADDIQSPEAEYVD  
LLLNPERYTGYKGPDAWKIWNVIYEENCFKPQTIKRPLNPLASGQGTSEENTFYSWLEGL  
CVEKRAFYRLISGLHASINVHLSARYLLQETWLEKKWGHNITEFQQRFDGILTEGEGPRR  
LKNLYFLYLIELRALSKVLPFFERPDFQLFTGNKIQDEENKMLLLEILHEIKSFPLHFDE  
NSFFAGDKKEAHKLKEDFRLHFRNISRIMDCVGCFCRLWGKLQTQGLGTALKILFSEKL  
IANMPESGPSYEFHLTRQEIVSLFNAFGRISTSVKELENFRNLLQNIH

**Important features:****Signal peptide:**

amino acids 1-23

**N-glycosylation site:**

amino acids 280-283 and 384-387

**Amidation site:**

amino acids 94-97

**Glycosaminoglycan attachment site:**

amino acids 20-23 and 223-226

**Aminotransferases class-V pyridoxal-phosphate:**

amino acids 216-222

**Interleukin-7 proteins:**

amino acids 338-343

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**FIGURE 101**

GCCTAGCCAGGCCAAGAATGCAATTGCCCGGTGGTGGGAGCTGGGAGACCCCTGTGCTT  
GGACGGGACAGGGTCGGGGGACACGCAGGATGAGCCCCGCGACCACTGGCACATTCTTG  
TGACAGTGTACAGTATTTCTCCAAGGTACACTCCGATCGGAATGTATACCCATCAGCAG  
GTGTCCTCTTTGTTTCATGTTTTGGAAAGAGAATATTTTAAGGGGAATTTCCACCTTACC  
CAAAACCTGGCGAGATTAGTAATGATCCCATAACATTTAATACAAATTTAATGGGTACC  
CAGACCGACCTGGATGGCTTCGATATATCCAAAGGACACCATATAGTGATGGAGTCCTAT  
ATGGGTCCCCAACAGCTGAAAATGTGGGGAAGCCAACAATCATTGAGATAACTGCCTACA  
ACAGGCGCACCTTTGAGACTGCAAGGCATAATTTGATAATTAATATAATGTCTGCAGAAG  
ACTTCCCGTTGCCATATCAAGCAGAATTCTTCATTAAGAATATGAATGTAGAAGAAATGT  
TGGCCAGTGAGGTTCTTGAGACTTTCTTGCGCAGTGAAAAATGTGTGGCAGCCAGAGC  
GCCTGAACGCCATAAACATCACATCGGCCCTAGACAGGGGTGGCAGGGTGCCACTTCCCA  
TTAATGACCTGAAGGAGGGCGTTTATGTTCATGGTTGGTGCAGATGTCCCGTTTTCTTCTT  
GTTTACGAGAAGTTGAAAATCCACAGAATCAATTGAGATGTAGTCAAGAAATGGAGCCTG  
TAATAACATGTGATAAAAAATTTTCGTACTCAATTTTACATTGACTGGTGCAAATTTTCAT  
TGGTTGATAAAACAAAGCAAGTGTCCACCTATCAGGAAGTGATTTCGTGGAGAGGGGATTT  
TACCTGATGGTGGAGAATACAAACCCCTTCTGATTCTTTGAAAAGCAGAGACTATTACA  
CGGATTTCTTAATTACACTGGCTGTGCCCTCGGCAGTGGCACTGGTCCTTTTTCTAATAC  
TTGCTTATATCATGTGCTGCCGACGGGAAGGCGTGGAAAAGAGAAACATGCAAACACCAG  
ACATCCAACCTGGTCCATCACAGTGCTATTCAGAAATCTACCAAGGAGCTTCGAGACATGT  
CCAAGAATAGAGAGATAGCATGGCCCCCTGTCAACGCTTCCTGTGTTCCACCTGTGACTG  
GGGAAATCATACCTCCTTTACACACAGACAACATATGATAGCACAAACATGCCATTGATGC  
AAACGCAGCAGAACTTGCCACATCAGACTCAGATTCCCCAACAGCAGACTACAGGTAAAT  
GGTATCCCTGAAGAAAGAAAACCTGACTGAAGCAATGAATTTATAATCAGACAATATAGCA  
GTTACATCACATTTCTTTCTCTTCCAATAATGCATGAGCTTTTCTGGCATATGTTATGC  
ATGTTGGCAGTATTAAGTGTATACCAATAATACAACATAACTTTCATTTTACTAATGTA  
TTTTTTTGTACTTAAAGCATTTTGTGACAATTTGTAAACATTGATGACTTTATATTTGTT  
ACAATAAAAGTTGATCTTTAAATAAATATTATTAATGAAGCCTAAAAAAAAAAAA

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**FIGURE 102**

MQLPRWWELGDPCAWTGQGRGTRRMSPATTGTFLLTVYSIFSKVHSDRNVYPSAGVLFVH  
VLEREYFKGEFPPYPKPGEISNDPITFNTNLMGYPDRLPGWLRYYIQRTPYSDGVLYGSPTA  
ENVGKPTIIIEITAYNRRTFETARHNLIIINIMSAEDFPLPYQAEFFIKNMNVEEMLASEVL  
GDFLGAVKNVWQPERLNAINITSALDRGGRVPLPINDLKEGVYVMVGADVPFSSCLREVE  
NPQNQLRCSQEMEPVITCDKKFRTQFYIDWCKISLVDKTKQVSTYQEVIRGEGILPDGGE  
YKPPSDSLKSRDYYTDFLITLAVPSAVALVFLILAYIMCCRREGVEKRNMQTPDIQLVH  
HSAIQKSTKELRDMSKNREIAWPLSTLPVFHPVTGEIIPPLHTDNYDSTNMPLMQTQQNL  
PHQTQIPQQQTGKWYP

**signal sequence:**

Amino acids 1-46

**transmembrane domain:**

Amino acids 319-338

**N-glycosylation site:**

Amino acids 200-204

**cAMP- and cGMP-dependent protein kinase phosphorylation site:**

Amino acids 23-27

**Tyrosine kinase phosphorylation site:**

Amino acids 43-52

**N-myristoylation sites:**

Amino acids 17-23;112-118;116-122;185-191

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**FIGURE 103**

CAGAAGAGGGGGCTAGCTAGCTGTCTCTGCGGACCAGGGAGACCCCCGCGCCCCCCCCGGT  
GTGAGGCGGCCTCACAGGGCCGGGTGGGCTGGCGAGCCGACGCGGCGGGAGGAGGCTG  
TGAGGAGTGTGTGGAACAGGACCCGGGACAGAGGAACCATGGCTCCGCAGAACCTGAGCA  
CCTTTTGCCTGTTGCTGCTATACCTCATCGGGGCGGTGATTGCCGGACGAGATTTCTATA  
AGATCTTGGGGGTGCCTCGAAGTGCCTCTATAAAGGATATTAAAAAGGCCTATAGGAAAC  
TAGCCCTGCAGCTTCATCCCGACCGGAACCTGATGATCCACAAGCCCAGGAGAAATTCC  
AGGATCTGGGTGCTGCTTATGAGGTTCTGTCAGATAGTGAGAAACGGAAACAGTACGATA  
CTTATGGTGAAGAAGGATTAAAAGATGGTCATCAGAGCTCCCATGGAGACATTTTTTTCAC  
ACTTCTTTGGGGATTTTGGTTTTCATGTTTGGAGGAACCCCTCGTCAGCAAGACAGAAATA  
TTCCAAGAGGAAGTGATATTATTGTAGATCTAGAAGTCACTTTGGAAGAAGTATATGCAG  
GAAATTTTGTGGAAGTAGTTAGAAACAAACCTGTGGCAAGGCAGGCTCCTGGCAAACGGA  
AGTGCAATTGTGCGCAAGAGATGCGGACCACCCAGCTGGGGCCCTGGGCGCTTCCAAATGA  
CCCAGGAGGTGGTCTGCGACGAATGCCCTAATGTCAAACCTAGTGAATGAAGAACGAACGC  
TGGAAGTAGAAATAGAGCCTGGGGTGAGAGACGGCATGGAGTACCCCTTTATTGGAGAAG  
GTGAGCCTCACGTGGATGGGGAGCCTGGAGATTTACGGTTCGAATCAAAGTTGTCAAGC  
ACCCAATATTTGAAAGGAGAGGAGATGATTTGTACACAAATGTGACAATCTCATTAGTTG  
AGTCACTGGTTGGCTTTGAGATGGATATTACTCACTTGGATGGTCACAAGGTACATATTT  
CCCGGGATAAGATCACCAGGCCAGGAGCGAAGCTATGGAAGAAAGGGGAAGGGCTCCCCA  
ACTTTGACAACAACAATATCAAGGGCTCTTTGATAATCACTTTTGATGTGGATTTTCCAA  
AAGAACAGTTAACAGAGGAAGCGAGAGAAGGTATCAAACAGCTACTGAAACAAGGGTCAG  
TGCAGAAGGTATACAATGGACTGCAAGGATATTGAGAGTGAATAAAATTGGACTTTGTTT  
AAAATAAGTGAATAAGCGATATTTATTATCTGCAAGGTTTTTTTTGTGTGTGTTTTTGT  
TTATTTTCAATATGCAAGTTAGGCTTAATTTTTTTTATCTAATGATCATCATGAAATGAAT  
AAGAGGGCTTAAGAATTTGTCCATTTGCATTCGGAAAAGAATGACCAGCAAAGGTTTAC  
TAATACCTCTCCCTTTGGGGATTTAATGTCTGGTGCTGCCGCCTGAGTTTCAAGAATTAA  
AGCTGCAAGAGGACTCCAGGAGCAAAAGAAACACAATATAGAGGGTTGGAGTTGTTAGCA  
ATTTCAATTCAAAATGCCAACTGGAGAAGTCTGTTTTTAAATACATTTTGTGTGTTATTTTA

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**FIGURE 104**

MAPQNLSTFCLLLLYLIGAVIAGRDFYKILGVPRASIKDIKKAYRKLALQLHPDRNPDD  
PQAQEKFDLGAAYEVLSDSEKRRQYDTYGEGLKDGHQSSHGDI FSHFFGDFGFMFGGT  
PRQQRNIPRGSDIIVDLEVTLEEYAGNFVEVVRNKPVARQAPGKRKCNCRQEMRTTQL  
GPGRFQMTQEVVCDPCPNVKLVNEERTLEVEIEPGVRDGM EYPFIGEGEPHVDGEPGDLR  
FRIKVVKHPIFERRGDDLYTNVTISLVESLVGFEMDITHLDGHKVHISRDKITRPGAKLW  
KKGEGLPNFDNNNIKGLIITFDVDFPKEQLTEEAREGIKQLLKQGSVQKVYNGLQGY

**Important features:**

**Signal peptide:**

amino acids 1-22

**Cell attachment sequence:**

amino acids 254-257

**Nt-dnaJ domain signature:**

amino acids 67-87

**Homologous region to Nt-dnaJ domain proteins:**

amino acids 26-58

**N-glycosylation site:**

amino acids 5-9, 261-265

**Tyrosine kinase phosphorylation site:**

amino acids 253-260

**N-myristoylation site:**

amino acids 18-24, 31-37, 93-99, 215-221

**Amidation site:**

amino acids 164-168



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**FIGURE 105**

GGCACGAGGCGGCGGGGCAGTCGCGGGATGCGCCCGGGAGCCACAGCCTGAGGCCCTCAG  
GTCTCTGCAGGTGTCGTGGAGGAACCTAGCACCTGCCATCCTCTTCCCCAATTTGCCACT  
TCCAGCAGCTTTAGCCCATGAGGAGGATGTGACCGGGACTGAGTCAGGAGCCCTCTGGAA  
GCATGGAGACTGTGGTGATTGTTGCCATAGGTGTGCTGGCCACCATCTTTCTGGCTTCGT  
TTGCAGCCTTGGTGCTGGTTTGCAGGCAGCGCTACTGCCGCGCGGAGACCCTGCTGCAGC  
GCTATGATTCTAAGCCCATTTGTGGACCTCATTGGTGCCATGGAGACCCAGTCTGAGCCCT  
CTGAGTTAGAACTGGACGATGTCGTTATCACCAACCCCCACATTGAGGCCATTCTGGAGA  
ATGAAGACTGGATCGAAGATGCCTCGGGTCTCATGTCCCACTGCATTGCCATCTTGAAGA  
TTTGTCACACTCTGACAGAGAAGCTTGTTGCCATGACAATGGGCTCTGGGGCCAAGATGA  
AGACTTCAGCCAGTGTGACGACATCATTGTGGTGGCCAAGCGGATCAGCCCCAGGGTGG  
ATGATGTTGTGAAGTCGATGTACCCTCCGTTGGACCCCCAAACTCCTGGACGCACGGACGA  
CTGCCCTGCTCCTGTCTGTGTCAGTCACCTGGTGCTGGTGACAAGGAATGCCTGCCATCTGA  
CGGGAGGCCTGGACTGGATTGACCAGTCTCTGTGCGGCTGCTGAGGAGCATTGGAAGTCC  
TTCGAGAAGCAGCCCTAGCTTCTGAGCCAGATAAAGGCCTCCCAGGCCCTGAAGGCTTCC  
TGCAGGAGCAGTCTGCAATTTAGTGCCTACAGGCCAGCAGCTAGCCATGAAGGCCCTGC  
CGCCATCCCTGGATGGCTCAGCTTAGCCTTCTACTTTTTCTATAGAGTTAGTTGTTCTC  
CACGGCTGGAGAGTTGAGCTGTGTGTGCATAGTAAAGCAGGAGATCCCCGTCAGTTTATG  
CCTCTTTTGCAGTTGCAAACTGTGGCTGGTGAGTGGCAGTCTAATACTACAGTTAGGGGA  
GATGCCATTCACTCTCTGCAAGAGGAGTATTGAAAACCTGGTGGACTGTCAGCTTTATTTA  
GCTCACCTAGTGTTTTCAAGAAAATTGAGCCACCGTCTAAGAAATCAAGAGGTTTCACAT  
TAAAATTAGAATTTCTGGCCTCTCTCGATCGGTGAGAATGTGTGGCAATTCTGATCTGCA  
TTTTCAGAAGAGGACAATCAATTGAAACTAAGTAGGGGTTTCTTCTTTTGGCAAGACTTG  
TACTCTCTCACCTGGCCTGTTTCATTTATTTGTATTATCTGCCTGGTCCCTGAGGCGTCT  
GGGTCTCTCCTCTCCCTTGCAGGTTTGGGTTTGAAGCTGAGGAACCTACAAAGTTGATGAT  
TTCTTTTTTATCTTTATGCCTGCAATTTTACCTAGCTACCACTAGGTGGATAGTAAATTT  
ATACTTATGTTTCCCTCAAAAAAAAAAAAAAA

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## FIGURE 106

METVVIVAIGVLATIFLASFAALVLVCRQRYCRPRDLLQRYDSKPIVDLIGAMETQSEPS  
ELELDDVVI TNPHIEAILENEDWIEDASGLMSHCIAILKI CHTLTEKLVAMTMGSGAKMK  
TSASVSDIIVVAKRISPRVDDVVKSMYPPLDPKLLDARTTALLSVSHLVLVTRNACHLT  
GGLDWIDQSLSAEEHLEVLREAALASEPDKGLPGPEGFLQEQSAI

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**FIGURE 107**

GCTTCATTTCTCCCGACTCAGCTTCCCACCCTGGGCTTTCCGAGGTGCTTTCGCCGCTGT  
CCCCACCACTGCAGCCATGATCTCCTTAACGGACACGCAGAAAATTGGAATGGGATTAAC  
AGGATTTGGAGTGTTTTTCCTGTTCTTTGGAATGATTCTCTTTTTTGACAAAGCACTACT  
GGCTATTGGAAATGTTTTATTTGTAGCCGGCTTGGCTTTTGTAATTGGTTTAGAAAGAAC  
ATTCAGATTCTTCTTCCAAAAACATAAAATGAAAGCTACAGGTTTTTTTTCTGGGTGGTGT  
ATTTGTAGTCCTTATTGGTTGGCCTTTGATAGGCATGATCTTCGAAATTTATGGATTTTT  
TCTCTTGTTCAAGGGGCTTCTTTCCTGTCGTTGTTGGCTTTATTAGAAGAGTGCCAGTCCT  
TGGATCCCTCCTAAATTTACCTGGAATTAGATCATTTGTAGATAAAGTTGGAGAAAGCAA  
CAATATGGTATAAACAACAAGTGAATTTGAAGACTCATTTAAATATTGTGTTATTTATAA  
AGTCATTTGAAGAATATTCAGCACAAAATTAAATTACATGAAATAGCTTGTAATGTTCTT  
TACAGGAGTTTAAACGTATAGCCTACAAAGTACCAGCAGCAAATTAGCAAAGAAGCAGT  
GAAAACAGGCTTCTACTCAAGTGAAC TAAGAAGAAGTCAGCAAGCAAAGTGAAGAGGTG  
AAATCCATGTTAATGATGCTTAAGAACTCTTGAAGGCTATTTGTGTTGTTTTTCCACAA  
TGTGCGAAACTCAGCCATCCTTAGAGAACTGTGGTGCCTGTTTCTTTTCTTTTATTTTG  
AAGGCTCAGGAGCATCCATAGGCATTTGCTTTTTAGAAAGTGTCCACTGCAATGGCAAAAA  
TATTTCCAGTTGCACTGTATCTCTGGAAGTGATGCATGAATTCGATTGGATTGTGTCATT  
TTAAAGTATTTAAACCAAGGAAACCCCAATTTTGATGTATGGATTACTTTTTTTTGNGCN  
CAGGGCC

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**FIGURE 108**

MISLTDTQKIGMGLTGFGVFFLFFGMILFFDKALLAIGNVLFVAGLAFVIGLERTFRFFF  
QKHKMKATGFFLGGVFVVLIGWPLIGMIFEIYGFFLLFRGFFPVVVGFIIRVPVLGSLN  
LPGIRSFVDKVGESNNMV

**Important features:****Transmembrane domains:**

amino acids 12-30 (typeII), 33-52, 69-89 and 93-109

**N-myristoylation sites:**

amino acids 11-16, 51-56 and 116-121

**Aminoacyl-transfer RNA synthetases class-II protein:**

amino acids 49-59

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**FIGURE 109**

CCAGTCTGTCGCCACCTCACTTGGTGTCTGCTGTCCCCGCCAGGCAAGCCTGGGGTGAGA  
GCACAGAGGAGTGGGCCGGGACCATGCGGGGGACGCGGCTGGCGCTCCTGGCGCTGGTGC  
TGGCTGCCTGCGGAGAGCTGGCGCCGGCCCTGCGCTGCTACGTCTGTCCGGAGCCCACAG  
GAGTGTCGGACTGTGTCACCATCGCCACCTGCACCACCAACGAAACCATGTGCAAGACCA  
CACTCTACTCCCGGGAGATAGTGTACCCCTTCCAGGGGGACTCCACGGTGACCAAGTCCT  
GTGCCAGCAAGTGTAAGCCCTCGGATGTGGATGGCATCGGCCAGACCCTGCCCCGTGTCCT  
GCTGCAATACTGAGCTGTGCAATGTAGACGGGGCGCCCGCTCTGAACAGCCTCCACTGCG  
GGGCCCTCACGCTCCTCCCACTCTTGAGCCTCCGACTGTAGAGTCCCCGCCCACCCCCAT  
GGCCCTATGCGGCCCAGCCCCGAATGCCTTGAAGAAGTGCCCCCTGCACCAGGAAAAAA  
AAAAA

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## FIGURE 110

MRGTRLALLALVLAACGELAPALRCYVCPEPTGVSDCVTIATCTTNETMCKTTLYSREIV  
YPFQGDSTVTKSCASKCKPSDVDGIGQTLFVSCCNTELCNVDGAPALNSLHCGALTLLPL  
LSLRL

**Important features:**

**Signal peptide:**

amino acids 1-17

**N-glycosylation site:**

amino acids 46-49

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## FIGURE 111

GCGCCGCCAGGCGTAGGCGGGGTGGCCCTTGCGTCTCCCGCTTCCTTGAAAAACCCGGCG  
GGCGAGCGAGGCTGCGGGCCGGCCGCTGCCCTTCCCCACACTCCCCGCCGAGAAGCCTCG  
CTCGGCGCCCAACATGGCGGGTGGGCGCTGCGGCCCCGAGCTAACGGCGCTCCTGGCCGC  
CTGGATCGCGGCTGTGGCGGCGACGGCAGGCCCCGAGGAGGCCGCGCTGCCGCCGGAGCA  
GAGCCGGGTCCAGCCCATGACCGCCTCCAACCTGGACGCTGGTGATGGAGGGCGAGTGGAT  
GCTGAAATTTTACGCCCCATGGTGTCCATCCTGCCAGCAGACTGATTGAGAATGGGAGGC  
TTTTGCAAAGAATGGTGAAATACTTCAGATCAGTGTGGGAAGGTAGATGTCATTCAAGA  
ACCAGGTTTGAGTGGCCGCTTCTTTGTCAACACTCTCCAGCATTTTTTTCATGCAAAGGA  
TGGGATATTCCGCCGTTATCGTGGCCCCAGGAATCTTCGAAGACCTGCAGAATTATATCTT  
AGAGAAGAAATGGCAATCAGTCGAGCCTCTGACTGGCTGGAAATCCCCAGCTTCTCTAAC  
GATGTCTGGAATGGCTGGTCTTTTTTAGCATCTCTGGCAAGATATGGCATCTTCACAACTA  
TTTCACAGTGACTCTTGGAATTCCTGCTTGGTGTTCTTATGTGTTTTTCGTCATAGCCAC  
CTTGTTTTTTGGCCTTTTTATGGGTCTGGTCTTGGTGGTAATATCAGAATGTTTCTATGT  
GCCACTTCCAAGGCATTTATCTGAGCGTTCTGAGCAGAATCGGAGATCAGAGGAGGCTCA  
TAGAGCTGAACAGTTGCAGGATGCGGAGGAGGAAAAAGATGATTCAAATGAAGAAGAAAA  
CAAAGACAGCCTTGTTAGATGATGAAGAAGAGAAAGAAGATCTTGGCGATGAGGATGAAGC  
AGAGGAAGAAGAGGAGGAGGACAACCTGGCTGCTGGTGTGGATGAGGAGAGAAGTGAGGC  
CAATGATCAGGGGCCCCCAGGAGAGGACGGTGTGACCCGGGAGGAAGTAGAGCCTGAGGA  
GGCTGAAGAAGGCATCTCTGAGCAACCTGCCAGCTGACACAGAGGTGGTGGAAAGACTC  
CTTGAGGCAGCGTAAAGTCAGCATGCTGACAAGGGACTGTAGATTTAATGATGCGTTTTT  
CAAGAATACACACCAAAACAATATGTCAGCTTCCCTTTGGCCTGCAGTTTTGTACCAAATC  
CTTAATTTTTCTGAATGAGCAAGCTTCTCTTAAAGATGCTCTCTAGTCATTTGGTCTC  
ATGGCAGTAAGCCTCATGTATACTAAGGAGAGTCTTCCAGGTGTGACAATCAGGATATAG  
AAAAACAAACGTAGTGTGGGATCTGTTTGGAGACTGGGATGGGAACAAGTTCATTTACT  
TAGGGGTGAGAGAGTCTCGACCAGAGGAGGCCATTCCCAGTCCTAATCAGCACCTTCCAG  
AGACAAGGCTGCAGGCCCTGTGAAATGAAAGCCAAGCAGGAGCCTTGGCTCCTGAGCATC  
CCCAAAGTGTAACGTAGAAGCCTTGCATCCTTTTCTTGTGTAAAGTATTTATTTTTGTCA  
AATTGCAGGAAACATCAGGCACCACAGTGCATGAAAAATCTTTCACAGCTAGAAATTGAA  
AGGGCCTTGGGTATAGAGAGCAGCTCAGAAATCATCCCAGCCCTCTGAATCTCCTGTGCT  
ATGTTTTATTTCTTACCTTTAATTTTTCCAGCATTTCCACCATGGGCATTTCAGGCTCTCC  
ACACTCTTCACTATTATCTCTTGGTCAGAGGACTCCAATAACAGCCAGGTTTACATGAAC  
TGTGTTTGTTCATTCTGACCTAAGGGGTTTAGATAATCAGTAACCATAACCCCTGAAGCT  
GTGACTGCCAAACATCTCAAATGAAATGTTGTGGCCATCAGAGACTCAAAAGGAAGTAAG  
GATTTTACAAGACAGATTAAAAAAAATTGTTTTGTCCAAAATATAGTTGTTGTTGATTT  
TTTTTTAAGTTTTCTAAGCAATATTTTTCAAGCCAGAAGTCCTCTAAGTCTTGCCAGTAC  
AAGGTAGTCTTGTGAAGAAAAGTTGAATACTGTTTTGTTTTCATCTCAAGGGGTTCCCTG  
GGTCTTGAACACTTTAATAATAACTAAAAAACCACTTCTGATTTTCTTTCAGTGATGTG  
CTTTTGGTGAAAGAATTAATGAACTCCAGTACCTGAAAGTGAAAGATTTGATTTTGTTC  
CATCTTCTGTAATCTTCCAAGAATTATATCTTTGTAAATCTCTCAATACTCAATCTACT  
GTAAGTACCCAGGGAGGCTAATTTCTTT

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**FIGURE 112**

MAGGRCGPQLTALLAAWIAAVAATAGPEEAALPPEQSRVQPMTASNWTLVMEGEWMLKFY  
APWCPSCQQT DSEWEAFKNGEILQISVGKVDV IQEPGLSGRFFVTTLPAFFHAKDGIFR  
RYRGP GIGFEDLQNYILEKKWQSVEPLTGWKSPASLTMSGMAGLFSISGKIWHLHNYFTVT  
LGIPAWCSYVFFVIATLVFGLFMGLVLVVISSECFYVPLPRHLSERSEQNRRSEEAHRAEQ  
LQDAEEEEKDDSN EEEENKDSLVDDEEEKEDLGDEDEAE EEEEEEDNLAAGVDEERSEANDQG  
PPGEDGVTREEVEPEEAEEGISEQPCPADTEVVEDSLRQRKSQHADKGL

**Important features:**

**Signal peptide:**

amino acids 1-22

**Transmembrane domain:**

amino acids 191-211

**N-glycosylation site:**

amino acids 46-49

**Thioredoxin family proteins:** (homologous region to disulfide isomerase)

amino acids 56-72

**Flavodoxin proteins:**

amino acids 173-187



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**FIGURE 113**

GAGGAACCTACCGGTACCGGCCGCGCGCTGGTAGTCGCCGGTGTGGCTGCACCTCACCAA  
TCCCGTGCGCCGCGCGCTGGGCCGTCGGAGAGTGCCTGTGCTTCTCTCCTGCACGCGGTGC  
TTGGGCTCGGCCAGGCGGGGTCCGCCGCCAGGGTTTGAGGATGGGGGAGTAGCTACAGGA  
AGCGACCCCGCGATGGCAAGGTATATTTTTGTGGAATGAAAAGGAAGTATTAGAAATGAG  
CTGAAGACCATTACAGATTAATATTTTTGGGGACAGATTTGTGATGCTTGATTACCCCT  
TGAAGTAATGTAGACAGAAGTTCTCAAATTTGCATATTACATCAACTGGAACCAGCAGTG  
AATCTTAATGTTCACTTAAATCAGAACTTGCATAAGAAAGAGAATGGGAGTCTGGTTAAA  
TAAAGATGACTATATCAGAGACTTGAAAAGGATCATTCTCTGTTTTCTGATAGTGTATAT  
GGCCATTTTAGTGGGCACAGATCAGGATTTTTACAGTTTACTTGGAGTGTCCAAAACCTGC  
AAGCAGTAGAGAAATAAGACAAGCTTTCAAGAAATTGGCATTGAAGTTACATCCTGATAA  
AAACCCGAATAACCCAAATGCACATGGCGATTTTTTAAAAATAAATAGAGCATATGAAGT  
ACTCAAAGATGAAGATCTACGGAATAAGTATGACAAATATGGAGAAAAGGGACTTGAGGA  
TAATCAAGGTGGCCAGTATGAAAGCTGGAAC TATTATCGTTATGATTTTGGTATTTATGA  
TGATGATCCTGAAATCATAACATTGGAAAAGAGAATTTGATGCTGCTGTTAATTCTGG  
AGAACTGTGGTTTTGTAAATTTTTACTCCCCAGGCTGTTCACTGCCATGATTTAGCTCC  
CACATGGAGAGACTTTGCTAAAGAAGTGGATGGGTACTTCTGAATTGGAGCTGTTAACTG  
TGGTGATGATAGAATGCTTTGCCGAATGAAAGGAGTCAACAGCTATCCCAGTCTCTTCAT  
TTTTCGGTCTGGAATGGCCCCAGTGAAATATCATGGAGACAGATCAAAGGAGAGTTTAGT  
GAGTTTTGCAATGCAGCATGTTAGAAGTACAGTGACAGAACTTTGGACAGGAAATTTTGT  
CAACTCCATACAACTGCTTTTGTCTGCTGGTATTGGCTGGCTGATCACTTTTTGTTCAA  
AGGAGGAGATTGTTTTGACTTCACAGACACGACTCAGGCTTAGTGGCATGTTGTTTTCTCA  
CTCATTTGGATGCTAAAGAAATATATTTGGAAGTAATACATAATCTTCCAGATTTTGAAC  
ACTTTCCGCAACACACTAGAGGATCGTTTGGCTCATCATCGGTGGCTGTTATTTTTTCA  
TTTTGGAATAAATGAAAATTCAAATGATCCTGAGCTGAAAAAACTAAAACTCTACTTAA  
AAATGATCATATTCAAGTTGGCAGGTTTACTGTTCTCTGCACCAGACATCTGTAGTAA  
TCTGTATGTTTTTTCAGCCGTCTCTAGCAGTATTTAAAGGACAAGGAACCAAAGAATATGA  
AATTCATCATGGAAAGAAGATTCTATATGATATACTTGCCTTTGCCAAAGAAAGTGTGAA  
TTCTCATGTTACCACGCTTGGACCTCAAAATTTTTCTGCCAATGACAAAGAACCATGGCT  
TGTTGATTTCTTTGCCCCCTGGTGTCCACCATGTGAGCTTTACTACCAGAGTTACGAAG  
AGCATCAAATCTTCTTTATGGTCAGCTTAAGTTTGGTACACTAGATTGTACAGTTTATGA  
GGGACTCTGTAACATGTATAACATTCAAGGCTTATCCAACAACAGTGGTATTCAACCAGTC  
CAACATTCATGAGTATGAAGGACATCACTCTGCTGAACAAATCTTGAGTTTCATAGAGGA  
TCTTATGAATCCTTCAGTGGTCTCCCTTACACCCACCACCTTCAACGAAGTAGTTACACA  
AAGAAAACACAACGAAGTCTGGATGGTTGATTTCTATTCTCCGTGGTGTATCCTTGCCA  
AGTCTTAATGCCAGAATGGAAAAGATGGCCCGGACATTAACTGGACTGATCAACGTGGG  
CAGTATAGATTGCCAACAGTATCATTTCTTTTTGTGCCCAGGAAAACGTTCAAAGATACCC  
TGAGATAAGATTTTTTCCCCCAAATCAAATAAAGCTTATCAGTATCACAGTTACAATGG  
TTGGAATAGGGATGCTTATTCCTGAGAATCTGGGGTCTAGGATTTTTACCTCAAGTATC  
CACAGATCTAACACCTCAGACTTTTCAGTGAAAAAGTTCTACAAGGGAAAAATCATTGGGT  
GATTGATTTCTATGCTCCTTGGTGTGGACCTTGCCAGAAATTTTGTCTCAGAAATTTGAGCT  
CTTGGCTAGGATGATTAAAGGAAAAGTGAAAGCTGGAAAAGTAGACTGTCAGGCTTATGC  
TCAGACATGCCAGAAAGCTGGGATCAGGGCTATCCAAC TGTAAAGTTTTATTTCTACGA  
AAGAGCAAAGAGAAATTTTCAAGAAGAGCAGATAAATAACCAGAGATGCAAAAAGCAATCGC  
TGCCTTAATAAGTGAAAAATTGAAAACCTCTCCGAAATCAAGGCAAGAGGAATAAGGATGA  
ACTTTGATAATGTTGAAGATGAAGAAAAAGTTTAAAGAAATCTTGACAGATGACATCAG  
AAGACACCTATTTAGAATGTTACATTTATGATGGGAATGAATGAACATTATCTTAGACTT

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GCAGTTGTACTGCCAGAATTATCTACAGCACTGGTGTAAAAGAAGGGTCTGCAAACCTTTT  
TCTGTAAAGGGCCGGTTTATAAATATTTTAGACTTTGCAGGCTATAATATATGGTTCACA  
CATGAGAACAAGAATAGAGTCATCATGTATTCTTTGTTATTTGCTTTTAAACAACCTTTAA  
AAAATATTAAACGATTCTTAGCTCAGAGCCATACAAAAGTAGGCTGGATTCCAGTCCATG  
GACCATAGATTGCTGTCCCCCTCGACGGACTTATAATGTTTCAGGTGGCTGGCTTGAACA  
TGAGTCTGCTGTGCTATCTACATAAATGTCTAAGTTGTATAAAGTCCACTTTCCCTTCAC  
GTTTTTTGGCTGACCTGAAAAGAGGTAACCTTAGTTTTTGGTCACTTGTTCTCCTAAAAAT  
GCTATCCCTAACCATATATTTATATTTTCGTTTTTAAAAACACCCATGATGTGGCACAGTAA  
ACAAACCCTGTTATGCTGTATTATTATGAGGAGATTCTTCATTGTTTTCTTTCTTCTCA  
AAGGTTGAAAAAATGCTTTTAAATTTTTTACAGCCGAGAAACAGTGCAGCAGTATATGTGC  
ACACAGTAAGTACACAAATTTGAGCAACAGTAAGTGCACAAATTCGTAGTTTGCTGTAT  
CATCCAGGAAAACCTGAGGGAAAAAATTATAGCAATTAAGTGGGCATTGTAGAGTATCC  
TAAATATGTTATCAAGTATTTAGAGTTCTATATTTTAAAGATATATGTGTTTCATGTATTT  
TCTGAAATTGCTTTTCATAGAAATTTTCCCACTGATAGTTGATTTTTGAGGCATCTAATAT  
TTACATATTTGCCTTCTGAACTTTGTTTTGACCTGTATCCTTTATTTACATTGGGTTTTT  
CTTTCATAGTTTTGGTTTTTCACTCCTGTCCAGTCTATTTATTATTCAAATAGGAAAAAT  
TACTTTACAGGTTGTTTTACTGTAGCTTATAATGATACTGTAGTTATTCCAGTTACTAGT  
TTACTGTCAGAGGGCTGCCTTTTTTCAGATAAATATTGACATAAATACTGAAGTTATTTTT  
ATAAGAAAATCAAGTATATAAATCTAGGAAAGGGATCTTCTAGTTTCTGTGTTGTTTAGA  
CTCAAAGAATCACAAATTTGTCAGTAACATGTAGTTGTTTAGTTATAATTCAGAGTGTAC  
AGAATGGTAAAAATTCCAATCAGTCAAAGAGGTCAATGAATTAAAAGGCTTGCAACTTT  
TTCAAAAAAAAAAAAAAAAAA

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**FIGURE 114**

MGVWLNKDDYIRDLKRIILCFLIVYMAILVGTDQDFYSL LGVSKTASSREIRQAFKKLAL  
KLHPDKNPNNPNAHGDFLKINRAYEVLKDEDLRKKYDKYGEKLEDNQGQYESWNYRY  
DFGIYDDDPEIITLERREFDAAVNSGELWVFVNFYSPGCSHCHDLAPTWRDFAKEVDGLLR  
IGAVNCGDDRMLCRMKGVN SYPSLFIFRSGMAPVKYHGDRSKESLVSFAMQHVRSTVTEL  
WTGNFVNSIQTAFAAGIGWLITFC SKGGDCLTSQTRLRLSGMLFLNSLDAKEIYLEVIHN  
LPDFELLSANTLEDRLAHRWLLFFHF GKKNENSNDPELKKLKTLLKNDHIQVGRFDCSSA  
PDICSNLYVFPQSLAVFKGQGTKEYEIHGKKILYDILAFAKESVNSHVTTLGPNFPAN  
DKEPWLVDFFAPWCPPCRALLPELRRASNLLYGQLKFGTLDCTVHEGLCNMYNIQAYPTT  
VVFNQSNIEYEGHSAEQILEFIEDLMNPSVVS LPTTFNELVTQRKHNEVWVDFYSP  
WCHPCQVLMPEWKRMARTLTGLINVGSIDCQQYHSFCAQENVQRYPEIRFFPPKSNKAYQ  
YHSYNGWNRDAYSRLRWGLGLPQVSTD LTPQTFSEKVLQGNHWVIDFYAPWCGPCQNF  
APEFELLARMIKGVKAGKVDCQAYAQCQAGIRAYPTVKFYFYERAKRNFQEEQINTR  
DAKAIAALISEKLETLRNQGRNKDEL

**Important features:**

**Endoplasmic reticulum targeting sequence:**

amino acids 744-747

**Cytochrome c family heme-binding site signature:**

amino acids 158-163

**Nt-dnaJ domain signature:**

amino acids 77-96

**N-glycosylation site:**

amino acids 484-487

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**FIGURE 115**

GCGGGCTGTTGACGGCGCTGCGATGGCTGCCTGCGAGGGCAGGAGAAGCGGAGCTCTCGG  
TTCCTCTCAGTCGGACTTCCTGACGCCGCCAGTGGGCGGGGCCCCCTTGGGCCGTGCCAC  
CACTGTAGTCATGTACCCACCGCCGCCGCCGCCCTCATCGGGACTTCATCTCGGTGAC  
GCTGAGCTTTGGCGAGAGCTATGACAACAGCAAGAGTTGGCGGGCGGCGCTCGTGCTGGAG  
GAAATGGAAGCAACTGTCGAGATTGCAGCGGAATATGATTCTCTTCCTCCTTGCCTTTCT  
GCTTTTCTGTGGACTCCTCTTCTACATCAACTTGGCTGACCATTGGAAAGCTCTGGCTTT  
CAGGCTAGAGGAAGAGCAGAAGATGAGGCCAGAAATTGCTGGGTAAAACAGCAAAATCC  
ACCCGTCTTACCAGCTCCTCAGAAGGCGGACACCGACCCCTGAGAACTTACCTGAGATTT  
GTCACAGAAGACACAAAGACACATCCAGCGGGGACCACCTCACCTGCAGATTAGACCCCC  
AAGCCAAGACCTGAAGGATGGGACCCAGGAGGAGGCCACAAAAGGCAAGAAGCCCCGTGT  
GGATCCCCGCCCCGAAGGAGATCCGCAGAGGACAGTCATCAGCTGGAGGGGAGCGGTGAT  
CGAGCCTGAGCAGGGCACCGAGCTCCCTTCAAGAAGAGCAGAAGTGCCACCAAGCCTCC  
CCTGCCACCGGCCAGGACACAGGGCACACCAGTGCATCTGAACTATCGCCAGAAGGGCGT  
GATTGACGTCTTCCTGCATGCATGGAAAGGATACCGCAAGTTTGCATGGGGCCATGACGA  
GCTGAAGCCTGTGTCCAGGTCTTCAGTGAGTGGTTTGGCCTCGGTCTCACACTGATCGA  
CGCGCTGGACACCATGTGGATCTTGGGTCTGAGGAAAGAATTTGAGGAAGCCAGGAAGTG  
GGTGTCTGAAGAAGTTACACTTTGAAAAGGACGTGGACGTCAACCTGTTTGGAGAGCACGAT  
CCGCATCCTGGGGGGGCTCCTGAGTGCCTACCACCTGTCTGGGGACAGCCTCTTCCTGAG  
GAAAGCTGAGGATTTTGGAAATCGGCTAATGCCTGCCTTCAGAACACCATCCAAGATTCC  
TACTCGGATGTGAACATCGGTACTGGAGTTGCCACCCGCCACGGTGGACCTCCGACAG  
CACTGTGGCCGAGGTGACCAGCATTAGCTGGAGTTCCGGGAGCTCTCCCGTCTCACAGG  
GGATAAGAAGTTTCAGGAGGCAGTGGAGAAGGTGACACAGCACATCCACGGCCTGTCTGG  
GAAGAAGGATGGGCTGGTGCCCATGTTTCATCAATACCCACAGTGGCCTCTTCACCCACCT  
GGGCGTATTACGCTGGGCGCCAGGGCCGACAGCTACTATGAGTACCTGCTGAAGCAGTG  
GATCCAGGGCGGGAAGCAGGAGACACAGCTGCTGGAAGACTACGTGGAAGCCATCGAGGG  
TGTCAGAACGCACCTGCTGCGGCACTCCGAGCCCAGTAAGCTCACCTTTGTGGGGGAGCT  
TGCCACCGGCCGCTTCAGTGCCAAGATGGACCACCTGGTGTGCTTCCTGCCAGGGACGCT  
GGCTCTGGGCGTCTACCACGGCCTGCCCGCCAGCCACATGGAGCTGGCCCAGGAGCTCAT  
GGAGACTTGTTACCAGATGAACCGGCAGATGGAGACGGGGCTGAGTCCCGAGATCGTGCA  
CTTCAACCTTTACCCCCAGCCGGGCCGTGGGACGTGGAGGTCAAGCCAGCAGACAGGCA  
CAACCTGCTGCGGCCAGAGACCGTGGAGAGCCTGTTCTACCTGTACCGCGTCACAGGGGA  
CCGCAAATACCAGGACTGGGGCTGGGAGATTCTGCAGAGCTTCAGCCGATTACACGGGT  
CCCCTCGGGTGGCTATTCTTCCATCAACAATGTCCAGGATCCTCAGAAGCCCCGAGCCTAG  
GGACAAGATGGAGAGCTTCTTCCTGGGGGAGACGCTCAAGTATCTGTTCTTGCTCTTCTC  
CGATGACCCAAACCTGCTCAGCCTGGACGCCTACGTGTTCAACACCGAAGCCCACCTCT  
GCCTATCTGGACCCCTGCCTAGGGTGGATGGCTGCTGGTGTGGGGACTTCGGGTGGGCAG  
AGGCACCTTGCTGGGTCTGTGGCATTTCCTCAAGGGCCACGTAGCACCGGCAACCGCCAA  
GTGGCCCAGGCTCTGAACTGGCTCTGGGCTCCTCCTCGTCTCTGCTTTAATCAGGACACC  
GTGAGGACAAGTGAGGCCGTGAGTCTTGGTGTGATGCGGGGTGGGCTGGGCCGCTGGAGC  
CTCCGCCTGCTTCCTCCAGAAGACACGAATCATGACTCACGATTGCTGAAGCCTGAGCAG  
GTCTCTGTGGGCCGACCAGAGGGGGGCTTCGAGGTGGTCCCTGGTACTGGGGTGACCGAG  
TGGACAGCCCAGGGTGCAGCTCTGCCCGGGCTCGTGAAGCCTCAGATGTCCCAATCCAA  
GGGTCTGGAGGGGCTGCCGTGACTCCAGAGGCCTGAGGCTCCAGGGCTGGCTCTGGTGT  
TACAAGCTGGACTCAGGGATCCTCCTGGCCGCCCCGAGGGGGCTTGAGGGGCTGGACGG  
CAAGTCCGTCTAGCTCACGGGCCCTCCAGTGGAATGGGTCTTTTCGGTGGAGATAAAAG  
TTGATTTGCTCTAACCGCAA

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**FIGURE 116**

MAACEGRRSGALGSSQSDFLTPPVGGAPWAVATTVMYPPPPPPPHRDFISVTLSFGESY  
DNSKSWRRRSCWRKWKQLSRLQRNMILFLLAFLLFCGLLFYINLADHWKALAFRLLEEEQK  
MRPEIAGLKPANPPVLPAPQKADTDPENLPEISSQKTQRHIQRGPPHLQIRPPSQDLKDG  
TQEEATKRQEAPVDPRPEGDPQRTVISWRGAVIEPEQGTLPSSRAEVPTKPPLPPARTQ  
GTPVHLNRYRQKGVIDVFLHAWKGYRKFAWGHDELKPVSRSFSEWFGLGLTLIDALDTMWI  
LGLRKEFEEARKWVSKKLHFEKDVDVNLFEISTIRILGGLLSAYHLSGDSLFLRKAEDFGN  
RLMPAFRTPSKIPYSDVNIGTGVAHPPRWTSDSTVAEVTSIQLEFRELSRLTGDKKFQEA  
VEKVTQHIHGLSGKKDGLVPMFINTHSGLFTHLGVFTLGARADSYEYLLKQWIOGGKQE  
TQLLEDYVEAIEGVRTHLLRHSEPSKLTFFVGE LAHGRFSAKMDHLVCFLPGTLALGVYHG  
LPASHMELAQELMETCYQMNRMETGLSPEIVHFNLYPQPGRRDVEVKPADRHNLRLPET  
VESLFYLYRVTGDRKYQDWGWEILQSFSRFRTRVPSGGYSSINNVQDPQKPEPRDKMESFF  
LGETLKYLFLLFSDDPNLLSLDAYVFNTTEAHPLPIWTPA

**Important features of the protein:**

**Transmembrane domain:**

amino acids 21-40 and 84-105 (type II)

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**FIGURE 117**

GTGGGATTTATTTGAGTGCAAGATCGTTTTCTCAGTGGTGGTGGGAAGTTGCCTCATCGCA  
GGCAGATGTTGGGGCTTTGTCCGAACAGCTCCCCTCTGCCAGCTTCTGTAGATAAGGGTT  
AAAACTAATATTTATATGACAGAAGAAAAAGATGTCATTCCGTAAAGTAAACATCATCA  
TCTTGGTCCTGGCTGTTGCTCTCTTCTTACTGGTTTTGCACCATAACTTCCTCAGCTTGA  
GCAGTTTGTAAAGGAATGAGGTTACAGATTGAGGAATGTAGGGCCTCAACCTATAGACT  
TTGTCCCAAATGCTCTCCGACATGCAGTAGATGGGAGACAAGAGGAGATTCCTGTGGTCA  
TCGCTGCATCTGAAGACAGGCTTGGGGGGGCCATTGCAGCTATAAACAGCATTTCAGCACA  
ACACTCGCTCCAATGTGATTTTCTACATTGTTACTCTCAACAATACAGCAGACCATCTCC  
GGTCTGGCTCAACAGTGATTCCCTGAAAAGCATCAGATACAAAATTGTCAATTTTGACC  
CTAAACTTTTGGAAGGAAAAGTAAAGGAGGATCCTGACCAGGGGGAATCCATGAAACCTT  
TAACCTTTGCAAGGTTCTACTTGCCAATTCTGGTTCCCAGCGCAAAGAAGGCCATATACA  
TGGATGATGATGTAATTGTGCAAGGTGATATTCTTGCCCTTTACAATACAGCACTGAAGC  
CAGGACATGCAGCTGCATTTTCAGAAGATTGTGATTGAGCCTCTACTAAAGTTGTCTATCC  
GTGGAGCAGGAAACCAGTACAATTACATTGGCTATCTTGACTATAAAAAGGAAAGAATTC  
GTAAGCTTTCCATGAAAGCCAGCACTTGCTCATTTAATCCTGGAGTTTTTGTGTGCAACC  
TGACGGAATGGAAACGACAGAATATAACTAACCAACTGGAAAAATGGATGAAACTCAATG  
TAGAAGAGGGACTGTATAGCAGAACCCCTGGCTGGTAGCATCACAAACACCTCCTCTGCTTA  
TCGTATTTTATCAACAGCACTCTACCATCGATCCTATGTGGAATGTCCGCCACCTTGTT  
CCAGTGCTGGAAAACGATATTCACCTCAGTTTGTAAGGCTGCCAAGTTACTCCATTGGA  
ATGGACATTTGAAGCCATGGGGAAGGACTGCTTCATATACTGATGTTTGGGAAAAATGGT  
ATATTCCAGACCCAACAGGCAAATTCACCTAATCCGAAGATATACCGAGATCTCAAACA  
TAAAGTGAAACAGAATTTGAACTGTAAGCAAGCATTTCTCAGGAAGTCCTGGAAGATAGC  
ATGCATGGGAAGTAACAGTTGCTAGGCTTCAATGCCTATCGGTAGCAAGCCATGGAAAAA  
GATGTGTCAGCTAGGTAAAGATGACAACTGCCCTGTCTGGCAGTCAGCTTCCCAGACAG  
ACTATAGACTATAAATATGTCTCCATCTGCCCTTACCAAGTGTTTTCTTACTACAATGCTG  
AATGACTGGAAAGAAGAACTGATATGGCTAGTTGAGCTAGCTGGTACAGATAATTCAAAA  
CTGCTGTTGGTTTTAATTTTGTAACCTGTGGCCTGATCTGTAAATAAACTTACATTTTC

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**FIGURE 118**

MSFRKVNIIILVLAVALFLLVLHHNFLSLSSLLRNEVTD SGIVGPQPIDFVPNALRHAVD  
GRQEEIPVVIAASEDRLGGAIAAINSIQHNTRS NVIFYIVTLNNTADHLRSWLNSDSLKS  
IRYKIVNFDPKLLEGKV KEDPDQGESMKPLTFARFYLPILVPSAKKAIYMDDDVIVQGDI  
LALYNTALKPGHAAAFSEDCDSASTKV VIRGAGNQYNYIGYLDYKKERIRKLSMKASTCS  
FNPGVFVANLTEWKRQ NITNQLEKWMKLNVEEGLYSRTL AGSITTPPLLIVFYQQHSTID  
PMWNVRLGSSAGKRYSPQFVKA AKLLHWNGHLKPWGRTASYTDVWEKWYIPDPTGKFNL  
IRRYTEISNIK

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**FIGURE 119**

CCATCCCTGAGATCTTTTTATAAAAAACCCAGTCTTTGCTGACCAGACAAAGCATAACCAG  
ATCTCACCAGAGAGTCGCAGACACTATGCTGCCTCCCATGGCCCTGCCCAGTGTGTCTG  
GATGCTGCTTTCCTGCCTCATTCTCCTGTGTGTCAGGTTCAAGGTGAAGAAACCCAGAAGGA  
ACTGCCCTCTCCACGGATCAGCTGTCCCAAAGGCTCCAAGGCCTATGGCTCCCCCTGCTA  
TGCCTTGTTTTTGTACCAAAATCCTGGATGGATGCAGATCTGGCTTGCCAGAAGCGGCC  
CTCTGGAAAACTGGTGTCTGTGCTCAGTGGGGCTGAGGGATCCTTCGTGTCTCTCCCTGGT  
GAGGAGCATTAGTAACAGCTACTCATACATCTGGATTGGGCTCCATGACCCACACAGGG  
CTCTGAGCCTGATGGAGATGGATGGGAGTGGAGTAGCACTGATGTGATGAATTACTTTGC  
ATGGGAGAAAAATCCCTCCACCATCTTAAACCCTGGCCACTGTGGGAGCCTGTCAAGAAG  
CACAGGATTTCTGAAGTGGAAGATTATAACTGTGATGCAAAGTTACCCTATGTCTGCAA  
GTTCAAGGACTAGGGCAGGTGGGAAGTCAGCAGCCTCAGCTTGGCGTGCAGCTCATCATG  
GACATGAGACCAGTGTGAAGACTCACCTGGAAGAGAATATTCTCCCCAACTGCCCTAC  
CTGACTACCTTGTCATGATCCTCCTTCTTTTTCTTTTTCTTCACCTTCATTTCAGGCTT  
TTCTCTGTCTTCCATGTCTTGAGATCTCAGAGAATAATAATAAAAATGTTACTTTATAAA  
AAAAAAAAAAAAAAAAAAAA



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## FIGURE 120

MLPPMALPSVSWMLLSCLILLCQVQGEETQKELPSPRISCPKGSKAYGSPCYALFLSPKS  
WMDADLACQKRPSGKLVSVLSGAEGSFVSSLVRSISNSYSYIWIGLHDPTQGSEPDGDGW  
EWSSTDVMNYFAWEKNPSTILNPGHCGSLSRSTGFLKWKDYNCDAKL PYVCKFKD

**Important features:**

**Signal peptide:**

amino acids 1-26

**C-type lectin domain signature:**

amino acids 146-171

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**FIGURE 121**

AAAGTTACATTTTCTCTGGAACCTCTCCTAGGCCACTCCCTGCTGATGCAACATCTGGGTT  
TGGGCAGAAAGGAGGGTGCTTCGGAGCCCCGCCCTTTCTGAGCTTCCTGGGCCGGCTCTAG  
AACAAATTCAGGCTTCGCTGCGACTCAGACCTCAGCTCCAACATATGCATTCTGAAGAAAG  
ATGGCTGAGATGGACAGAATGCTTTATTTTGGAAAGAAACAATGTTCTAGGTCAAACCTGA  
GTCTACCAAATGCAGACTTTTACAATGGTTCTAGAAGAAATCTGGACAAGTCTTTTCATG  
TGGTTTTTCTACGCATTGATTCCATGTTTGTCTCACAGATGAAGTGGCCATTCTGCCTGCC  
CCTCAGAACCTCTCTGTACTCTCAACCAACATGAAGCATCTCTTGATGTGGAGCCCAGTG  
ATCGCGCCTGGAGAAACAGTGTACTATTCTGTCTGAATACCAGGGGGAGTACGAGAGCCTG  
TACACGAGCCACATCTGGATCCCCAGCAGCTGGTGCTCACTCACTGAAGGTCCTGAGTGT  
GATGTCACTGATGACATCACGGCCACTGTGCCATACAACCTTCGTGTGAGGGCCACATTG  
GGCTCACAGACCTCAGCCTGGAGCATCCTGAAGCATCCCTTTAATAGAAACTCAACCATC  
CTTACCCGACCTGGGATGGAGATCACCAAGATGGCTTCCACCTGGTTATTGAGCTGGAG  
GACCTGGGGCCCCAGTTTGAGTTCCTTGTGGCCTACTGGAGGAGGGAGCCTGGTGCCGAG  
GAACATGTCAAAATGGTGAGGAGTGGGGGTATTCCAGTGCACCTAGAAACCATGGAGCCA  
GGGGCTGCATACTGTGTGAAGGCCCAGACATTCGTGAAGGCCATTGGGAGGTACAGCGCC  
TTCAGCCAGACAGAATGTGTGGAGGTGCAAGGAGAGGCCATTCCCCTGGTACTGGCCCTG  
TTTGCCTTTGTTGGCTTCATGCTGATCCTTGTGGTTCGTGCCACTGTTTCGTCTGGAAAATG  
GGCCGGCTGCTCCAGTACTCCTGTTGCCCGTGGTGGTCCCTCCAGACACCTTGAAAATA  
ACCAATTCACCCAGAAAGTTAATCAGCTGCAGAAGGGAGGAGGTGGATGCCTGTGCCACG  
GCTGTGATGTCTCCTGAGGAACCTCAGGGCCTGGATCTCATAGGTTTGCAGGAAGGGCC  
CAGGTGAAGCCGAGAACCTGGTCTGCATGACATGGAAACCATGAGGGGACAAGTTGTGTT  
TCTGTTTTCCGCCACGGACAAGGGATGAGAGAAGTAGGAAGAGCCTGTTGTCTACAAGTC  
TAGAAGCAACCATCAGAGGCAGGGTGGTTTTGTCTAACAGAACACTGACTGAGGCTTAGGG  
GATGTGACCTCTAGACTGGGGGCTGCCACTTGCTGGCTGAGCAACCCTGGGAAAAGTGAC  
TTCATCCCTTCGGTCCCTAAGTTTTCTCATCTGTAATGGGGGAATTACCTACACACCTGCT  
AAACACACACACACAGAGTCTCTCTATATATACACACGTACACATAAATACACCCAGC  
ACTTGCAAGGCTAGAGGGAAAAGTGGTGACACTCTACAGTCTGACTGATTTCAGTGTTTTCTG  
GAGAGCAGGACATAAATGTATGATGAGAATGATCAAGGACTCTACACACTGGGTGGCTTG  
GAGAGCCCACTTTCCCAGAATAATCCTTGAGAGAAAAGGAATCATGGGAGCAATGGTGTT  
GAGTTCACTTCAAGCCCAATGCCGGTGCAGAGGGGAATGGCTTAGCGAGCTCTACAGTAG  
GTGACCTGGAGGAAGGTACAGCCACACTGAAAATGGGATGTGCATGAACACGGAGGATC  
CATGAACTACTGTAAAGTGTGACAGTGTGTGCACACTGCAGACAGCAGGTGAAATGTAT  
GTGTGCAATGCGACGAGAATGCAGAAAGTCAGTAACATGTGCATGTTTGTGTGCTCCTTT  
TTTCTGTTGGTAAAGTACAGAATTCAGCAAATAAAAAGGGCCACCCTGGCCAAAAGCGGT  
AAAAAAAAAAAAAAAA

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**FIGURE 122**

MQTFTMVLEEIWTSLEFMWFFYALIPCLLTDEVAILPAPQNLSVLSTNMKHELLMWSPVIAP  
GETVYYSVEYQGEYESLYTSHIWIPSSWCSLTEGPECDVTDDITATVPYNLRVRATLGSQ  
TSAWSILKHFPFNRNSTILTRPGMEITKDG FHLVIELEDLGPQFEFLVAYWRREPGAEHV  
KMVRSGGIPVHLETMEPGAAYCVKAQTFVKAIGRYSAFSQTECVEVQGEAIPLVLALFAF  
VGFMLILVVVPLFVWKMGRLLQYSCCPVVLPDTLKITNSPQKLISCRREEVDACATAVM  
SPEELLRAWIS

**Important features:****Signal peptide:**

amino acids 1-29

**Transmembrane domain:**

amino acids 230-255

**N-glycosylation sites:**

amino acids 40-43 and 134-137

**Tissue factor proteins homology:**

amino acids 92-119

**Integrins alpha chain protein homology:**

amino acids 232-262

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**FIGURE 123**

CGGACGCGTGGGCGGCCACCTCCGGAACAAGCCATGGTGGCGGCGACGGTGGCAGCGGCG  
TGGCTGCTCCTGTGGGCTGCGGCCTGCGCGCAGCAGGAGCAGGACTTCTACGACTTCAAG  
GCGGTCAACATCCGGGGCAAACCTGGTGTGCTGGAGAAGTACCGCGGATCGGTGTCCCTG  
GTGGTGAATGTGGCCAGCGAGTGC GGCTTCACAGACCAGCACTACCGAGCCCTGCAGCAG  
CTGCAGCGAGACCTGGGCCCCCACCACCTTTAAAGTGCTCGCCTTCCCCCTGCAACCAGTTT  
GGCCAACAGGAGCCTGACAGCAACAAGGAGATTGAGAGCTTTGCCCCGCCGCACCTACAGT  
GTCTCATTCCCCATGTTTAGCAAGATTGCAGTCACCGGTACTGGTGCCCATCCTGCCTTC  
AAGTACCTGGCCCAGACTTCTGGGAAGGAGCCCACCTGGAACCTTCTGGAAGTACCTAGTA  
GCCCCAGATGGAAAGGTGGTAGGGGCTTGGGACCCAACTGTGTCAAGTGGAGGAGGTCAGA  
CCCCAGATCACAGCGCTCGTGAGGAAGCTCATCCTACTGAAGCGAGAAGACTTATAACCA  
CCGCGTCTCCTCCTCCACCACCTCATCCCGCCCACCTGTGTGGGGCTGACCAATGCAAAC  
TCAAATGGTGCTTCAAAGGGAGAGACCCACTGACTCTCCTTCCCTTTACTCTTATGCCATT  
GGTCCCATCATTCTTGTGGGGGAAAAATTCTAGTATTTTGATTATTTGAATCTTACAGCA  
ACAAATAGGAACCTCCTGGCCAATGAGAGCTCTTGACCAGTGAATCACCAGCCGATACGAA  
CGTCTTGCCAACAAAAATGTGTGGCAAATAGAAGTATATCAAGCAATAATCTCCCACCCA  
AGGCTTCTGTAAACTGGGACCAATGATTACCTCATAGGGCTGTTGTGAGGATTAGGATGA  
AATACCTGTGAAAGTGCCTAGGCAGTGCCAGCCAAATAGGAGGCATTCAATGAACATTTT  
TTGCATATAAACCAAAAAATACTTGTTATCAATAAAAACTTGCAATCCAACATGAATTTT  
CAGCCGATGATAATCCAGGCCAAAGGTTTAGTTGTTGTTATTTCTCTGTATTATTTTCT  
TCATTACAAAAGAAATGCAAGTTCATTGTAACAATCCAAACAATACCTCACGATATAAAA  
TAAAAATGAAAGTATCCTCCTCAAAA

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## FIGURE 124

MVAATVAAAWLLLWAAACAQQEQDFYDFKAVNIRGKLVSLVKYRGSVSLVNVASECGFT  
DQHYRALQQQLQRD LGPHHFNVLA FPCNQFGQQEPDSNKEIESFARRTYSVSFPMFSKIAV  
TGTGAHPAFKYLAQTSGKEPTWNFWKYL VAPDGKVVGAWDPTVSVEEVRPQITALVRKLI  
LLKREDL

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**FIGURE 125**

CGGACGCGTGGGCGGACGCGTGGGCGGACGCGTGGGTTGGGAGGGGGCAGGATGGGAGGG  
AAAGTGAAGAAAACAGAAAAGGAGAGGGACAGAGGCCAGAGGACTTCTCATACTGGACAG  
AAACCGATCAGGCATGGAACTCCCCCTTCGTCACTCACCTGTTCTTGCCCCCTGGTGTTCCT  
GACAGGTCTCTGCTCCCCCTTTAACCTGGATGAACATCACCCACGCCTATTCCCAGGGCC  
ACCAGAAGCTGAATTTGGATACAGTGTCTTACAACATGTTGGGGGTGGACAGCGATGGAT  
GCTGGTGGGCGCCCCCTGGGATGGGCCTTCAGGCGACCGGAGGGGGGACGTTTATCGCTG  
CCCTGTAGGGGGGGCCCAATGCCCATGTGCCAAGGGCCACTTAGGTGACTACCAACT  
GGGAAATTCATCTCATCCTGCTGTGAATATGCACCTGGGGATGTCTCTGTTAGAGACAGA  
TGGTGATGGGGGATTTCATGGTGAGCTAAGGAGAGGGTGGTGGCAGTGTCTCTGAAGGTCC  
ATAAAAGAAAAAAGAGAAGTGTGGTAAGGGAAAATGGTCTGTGTGGAGGGGTCAAGGAGT  
TAAAAACCCTAGAAAGCAAAGGTAGGTAATGTCAGGGAGTAGTCTTCATGCCTCCTTCA  
ACTGGGAGCATGTTCTGAGGGTGCCCTCCCAAGCCTGGGAGTAACTATTTCCCCCATCCC  
CAGGCCTGTGCCCCCTCTCTGGTCTCGTGCTTGTGGCAGCTCTGTCTTCAGTTCTGGGATA  
TGTGCCCCGTGTGGATGCTTCATTCCAGCCTCAGGGAAGCCTGGCACCCACTGCCCAACGT  
GAGCCAGAGGAAGGCTGAGTACTTGGTTCCCAGAAGGAGATACTGGGTGGGAAAAAGATG  
GGGCAAAGCGGTATGATGCCTGGCAAAGGGCCTGCATGGCTATCCTCATTGCTACCTAAT  
GTGCTTGCAAAGCTCCATGTTTCCTAACAGATTTCAGACTCCTGGCCAGGTGTGGTGGCC  
CACACCTGTAAATTCAGCACTTTGGGAGGCCAAGGTGGGCAGATCACTTGAGGTGAGGAG  
TTCAAGACCAGCCTGGCCAACATGGTGAACTCCATCTCTACTAAAAAATAAATAAATAA  
AAAATTAGCTGGGTGCGCTAGTGATGCCTGTAATCTCATCTACTCGGGAGGCTAAGACA  
GGAGACTCTCACTTCAACCCAGGAGGTGGAGGTTGCGGTGAGCCAAGATTGTGCCTCTGC  
ACTCTAGCGTGGGTGACAGAGTAAGCGAGACTCCATCTCAAAAATAATAATAATAAAT  
TCAGACTCCTTATCAGGAGTCCATGATCTGGCCTGGCACAGTAACTCATGCCTGTAATCC  
CAACATTTTGGGAGGCCAACGCAGGAGGATTGCTTGAGGTCTGGAGGTTTGAGACCAGCC  
TGGGCAACATAGAAAGACCCCATCTCTAAATAAATGTTTTAAAAAT

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## FIGURE 126

MELPFVTHLFLPLVFLTGLCSPFNLDEHHPRLFPGPPEAEFGYSVLQHVGGGQRWMLVGA  
PWDGPGDRRGDVYRCPVGGAHNAPCAKHLGDYQLGNSSHPAVNMHLGMSLLETGDGG  
FMVS

**Important features:**

**Signal peptide:**

amino acids 1-22

**Cell attachment sequence:**

amino acids 70-73

**N-glycosylation site:**

amino acids 98-101

**Integrins alpha chain proteins:**

amino acids 67-81

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**FIGURE 127**

GAGAGGACGAGGTGCCGCTGCCTGGAGAATCCTCCGCTGCCGTCGGCTCCCGGAGCCCAG  
CCCTTTCCTAACCCAACCCAACCTAGCCCAGTCCCAGCCGCCAGCGCCTGTCCCTGTCAC  
GGACCCCAGCGTTACCATGCATCCTGCCGCTCTTCCTATCCTTACCCGACCTCAGATGCTC  
CCTTCTGCTCCTGGTAACTTGGGTTTTTACTCCTGTAACAACCTGAAATAACAAGTCTTG  
TACAGAGAATATAGATGAAATTTTAAACAATGCTGATGTTGCTTTAGTAAATTTTTATGC  
TGA CTGGTGTGCTTTT CAGTCAGATGTTGCATCCAATTTT TGAGGAAGCTTCCGATGTCAT  
TAAGGAAGAATTTCCAAATGAAAATCAAGTAGTGTGTTGCCAGAGTTGATTGTGATCAGCA  
CTCTGACATAGCCCAGAGATAACAGGATAAGCAAATACCCAACCCCTCAAATTGTTTTCGTAA  
TGGGATGATGATGAAGAGAGAATACAGGGGTCAGCGATCAGTGAAAGCATTGGCAGATTA  
CATCAGGCAACAAAAAAGTGACCCATTCAAGAAATTCGGGACTTAGCAGAAATCACCAC  
TCTTGATCGCAGCAAAAGAAATATCATTGGATATTTTGAGCAAAAGGACTCGGACAAC  
TAGAGTTTTTTGAACGAGTAGCGAATATTTTGCATGATGACTGTGCCTTTCTTCTGCATT  
TGGGGATGTTTTCAAACCGGAAAGATATAGTGGCGACAACATAATCTACAAACCACCAGG  
GCATTCTGCTCCGGATATGGTGTACTTGGGAGCTATGACAAATTTTGATGTGACTTACAA  
TTGGATTCAAGATAAATGTGTTCTTGTCCGAGAAATAACATTTGAAAATGGAGAGGA  
ATTGACAGAAGAAGGACTGCCTTTTCTCATACTCTTTCACATGAAAGAAGATACAGAAAG  
TTTAGAAATATTCCAGAATGAAGTAGCTCGGCAATTAATAAGTGAAAAAGGTACAATAAA  
CTTTTTTACATGCCGATTGTGACAAATTTAGACATCCTCTTCTGCACATACAGAAAACCTC  
AGCAGATTGTCTGTAAATCGCTATTGACAGCTTTAGGCATATGTATGTGTTTGGGAGACTT  
CAAAGATGTATTAATTCCTGGAAAACTCAAGCAATTCGTATTTGACTTACATTCTGGAAA  
ACTGCACAGAGAATTCCATCATGGACCTGACCCAACTGATACAGCCCCAGGAGAGCAAGC  
CCAAGATGTAGCAAGCAGTCCACCTGAGAGCTCCTTCCAGAACTAGCACCCAGTGAATA  
TAGGTATACTCTATTGAGGGATCGAGATGAGCTTTTAAAAACTTGAAAAACAGTTTGTAAG  
CCTTTCAACAGCAGCATCAACCTACGTGGTGGAATAGTAAACCTATATTTTCATAATTC  
TATGTGTATTTTTATTTTGAATAAACAGAAAGAAATTTAAAAAAAAAAAAAAAAAAAAAA  
AAAAAAAAAAAAAAAAAAAAAAAAAAAA



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**FIGURE 128**

MHPAVFLSLPDLRCSLLLLVTWVFTPVTTEITSLATENIDEILNNADVALVNFYADWCRF  
SQMLHPIFEEASDVIKEEFPNENQVVFARVDCDQHSDIAQRYRISKYPTLKLFRNGMMMK  
REYRGQRSVKALADYIRQQKSDPIQEIRDLAEITTLDRSKRNIIGYFEQKSDNYRVFER  
VANILHDDCAFLSAFGDVSKPERYSGDNIYKPPGHSAPDMVYLGAMTNFDVTYNWIQDK  
CVPLVREITFENGEEELTEGLPFLILFHMKEDTESLEIFQNEVARQLISEKGTINFLHAD  
CDKFRHPLLHIQKTPADCPVIAIDSFRHMYVFGDFKDVLI PGKLKQFVFDLHSGKLHREF  
HHGPDPTDTAPGEQAQDVASSPPESSFQKLAPSEYRYTLLRDRDEL

**Important features:**

**Signal peptide:**

amino acids 1-29

**Endoplasmic reticulum targeting sequence:**

amino acids 403-406

**Tyrosine kinase phosphorylation site:**

amino acids 203-211

**Thioredoxin family proteins:**

amino acids 50-66

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**FIGURE 129**

GAGCAGGACGGAGCCATGGACCCCGCCAGGAAAGCAGGTGCCCAGGCCATGATCTGGACT  
GCAGGCTGGCTGCTGCTGCTGCTGCTTCGCGGAGGAGCGCAGGCCCTGGAGTGCTACAGC  
TGCGTGACAGAAAGCAGATGACGGATGCTCCCCGAACAAGATGAAGACAGTGAAGTGCGCG  
CCGGGCGTGACGTCTGCACCGAGGCCGTGGGGGCGGTGGAGACCATCCACGGACAATTC  
TCGCTGGCAGTGCGGGGTTGCGGTTTCGGGACTCCCCGGCAAGAATGACCGCGGCCTGGAT  
CTTCACGGGCTTCTGGCGTTCATCCAGCTGCAGCAATGCGCTCAGGATCGCTGCAACGCC  
AAGCTCAACCTCACCTCGCGGGCGCTCGACCCGGCAGGTAATGAGAGTGCTATACCCGCCC  
AACGGCGTGAGTGCTACAGCTGTGTGGGCCTGAGCCGGGAGGCGTGCCAGGGTACATCG  
CCGCCGGTCGTGAGCTGCTACAACGCCAGCGATCATGTCTACAAGGGCTGCTTCGACGGC  
AACGTCACCTTGACGGCAGCTAATGTGACTGTGTCTTGCCTGTCCGGGGCTGTGTCCAG  
GATGAATTCTGCACTCGGGATGGAGTAACAGGCCCAGGGTTCACGCTCAGTGGCTCCTGT  
TGCCAGGGGTCCCGCTGTAACCTCTGACCTCCGCAACAAGACCTACTTCTCCCCTCGAATC  
CCACCCCTTGTCCGGCTGCCCCCTCCAGAGCCCACGACTGTGGCCTCAACCACATCTGTC  
ACCACTTCTACCTCGGCCCCAGTGAGACCCACATCCACCACCAAAACCCATGCCAGCGCCA  
ACCAGTCAGACTCCGAGACAGGGAGTAGAACACGAGGCCTCCCGGGATGAGGAGCCCAGG  
TTGACTGGAGGCGCCGCTGGCCACCAGGACCGCAGCAATTCAGGGCAGTATCCTGCAAAA  
GGGGGGCCCCCAGCAGCCCCATAATAAAGGCTGTGTGGCTCCACAGCTGGATTGGCAGCC  
CTTCTGTTGGCCGTGGCTGCTGGTGTCTTCTACTGTGAGCTTCTCCACCTGGAAATTTCCCT  
CTCACCTACTTCTCTGGCCCTGGGTACCCCTCTTCTCATCACTTCCTGTTCCCACCACTG  
GACTGGGCTGGCCCAGCCCCTGTTTTTCCAACATTCGCCAGTATCCCCAGCTTCTGCTGC  
GCTGGTTTTGCGGCTTTGGGAAATAAAATACCGTTGTATATATTCTGCCAGGGGTGTTCTA  
GCTTTTTGAGGACAGCTCCTGTATCCTTCTCATCCTTGTCTCTCCGCTTGTCTCTTGTG  
ATGTTAGGACAGAGTGAGAGAAGTCAGCTGTCACGGGGAAGGTGAGAGAGAGGATGCTAA  
GCTTCCTACTCACTTTCTCCTAGCCAGCCTGGACTTTGGAGCGTGGGGTGGGTGGGACAA  
TGGCTCCCCACTCTAAGCACTGCCTCCCCTACTCCCCGCATCTTTGGGGAATCGGTTCCC  
CATATGTCTTCTTACTAGACTGTGAGCTCCTCGAGGGGGGGCCCCGTACCCAATTCGCC  
CTATAGTGAGTCGTA

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**FIGURE 130**

MDPARKAGAQAMIWTAGWLLLLLLRGGAQALECYSCVQKADDGCS PNKMKT VKCAPGVDV  
CTEAVGAVETIHGQFSLAVRGCGSGLPGKNDRGLDLHGLLAFIQLQQCAQDRCNAKLNLT  
SRALDPAGNESAYPPNGVECYSCVGLSREACQGTSPPVVSCYNASDHVYKGCDFDGNVTLT  
AANVTVSLPVRGCVQDEFCTRDGVTGPGFTLSGCCQGSRCNSDLRNKTYFSPRI PPLVR  
LPPPEPTTVASTTSVTTST SAPVRPTSTTKPMPAPTSQT PRQGEHEASRDEEPRLTGGA  
AGHQDRSNSGQYPAKGGPQQPHNKGCVAPTAGLAALLLAVAAGVLL

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**FIGURE 131**

AAACTTGACGCCATGAAGATCCCGGTCCTTCCTGCCGTGGTGCTCCTCTCCCTCCTGGTG  
CTCCACTCTGCCCAGGGAGCCACCCTGGGTGGTCCTGAGGAAGAAAGCACCATTGAGAAT  
TATGCGTCACGACCCGAGGCCTTTAACACCCCGTTCTTGAACATCGACAAATTGCGATCT  
GCGTTTAAGGCTGATGAGTTCCTGAACTGGCAGCCCTCTTTGAGTCTATCAAAAGGAAA  
CTTCCTTTCCTCAACTGGGATGCCTTTCCTAAGCTGAAAGGACTGAGGAGCGCAACTCCT  
GATGCCCAGTGACCATGACCTCCACTGGAAGAGGGGGCTAGCGTGAGCGCTGATTCTCAA  
CCTACCATAACTCTTTCCTGCCTCAGGAACTCCAATAAAACATTTTCATCCAAA

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## FIGURE 132

MKIPVLPVAVLLSLLVLHSAQGATLGGPEEESTIENYASRPEAFNTPFLNIDKLRSAFKA  
DEFLNWHALFESIKRKLPFLNWDAFPKLKGLRSATPDAQ

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**FIGURE 133**

CAGTTCTGAAATCAATGGAGTTAATTTAGGGAATACAAACCAGCCATGGGGGTGGAGATT  
GCCTTTGCCTCAGTGATTCTCACCTGCCTCTCCCTTCTGGCAGCAGGAGTCTCCCAGGTT  
GTTCTTCTCCAGCCAGTCCAACCTCAGGAGACAGGTCCAAGGCCATGGGAGATCTCTCC  
TGTGGCTTTGCCGGCCACTCATGAGAGTGTTTTTGTGTAAAGTATTTTTTTAGAATACTGT  
TGAATTCCTCATGATTTAATAACCATCCTTTGCCGAAGTTTTATGAGGCTTTAGGGGAATG  
TCAACCCTCAAATTTTTGTTATACTAGATGGCTTCCATTTACCCACCACTATTTTAAGGT  
CCCTTTATTTTTTAGGTTCAAGGTTCAATTTGACTTGAGAAAGTGCCCTTCTGCAGCTTCAT  
TGATTTTGTTTATCTTCACTATTAATTGTAACGATTAAAAAAGAAATAAGAGCACGCAGAC  
CTCTAGGAGAATATTTTTATCCCTGGGTGCCCCTGACACATTTATGTAGTGATCCCACAAA  
TGTGATTGTTAATTTAAATGTTATTCTAATATTAGTACATTCAGTTGTGATGTAATATGA  
ATAACCAGAATCTATTTCTTAAAAGTTTTGAGTATATTTTTCAACTAGATATTTGTATAG  
AAAGACTGAATAGTGATG

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## FIGURE 134

MGVEIAFASVILTCLSLAAGVSQVLLQPVPTQETGPKAMGDLSCGFAGHS

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**FIGURE 135**

GGGGAATCTGCAGTAGGTCTGCCGGCGATGGAGTGGTGGGCTAGCTCGCCGCTTCGGCTC  
TGGCTGCTGTTGTTCCCTGCCCTCAGCGCAGGGCCGCCAGAAGGAGTCAGGTTCAAAA  
TGGAAAGTATTTATTGACCAAATTAACAGGTCTTTGGAGAATTACGAACCATGTTCAAGT  
CAAACTGCAGCTGCTACCATGGTGT CATAGAAGAGGATCTAACTCCTTCCGAGGAGGC  
ATCTCCAGGAAGATGATGGCAGAGGTAGTCAGACGGAAGCTAGGGACCCACTATCAGATC  
ACTAAGAACAGACTGTACCGGGAAAATGACTGCATGTTCCCCTCAAGGTGTAGTGGTGT  
GAGCACTTTATTTTGGAAAGTGATCGGGCGTCTCCCTGACATGGAGATGGTGATCAATGTA  
CGAGATTATCCTCAGGTTCCCTAAATGGATGGAGCCTGCCATCCCAGTCTTCTCCTTCAGT  
AAGACATCAGAGTACCATGATATCATGTATCCTGCTTGGACATTTTGGGAAGGGGGACCT  
GCTGTTTGGCCAATTTATCCTACAGGTCTTGGACGGTGGGACCTCTTCAGAGAAGATCTG  
GTAAGGTGAGCAGCACAGTGGCCATGGAAAAAGAAAACTCTACAGCATATTTCCGAGGA  
TCAAGGACAAGTCCAGAACGAGATCCTCTCATTTCTTCTGTCTCGGAAAAACCCAAAACCTT  
GTTGATGCAGAATAACACCAAAAACAGGCCTGGAAATCTATGAAAGATACCTTAGGAAAG  
CCAGCTGCTAAGGATGTCCATCTTGTGGATCACTGCAAATACAAGTATCTGTTTAAATTTT  
CGAGGCGTAGCTGCAAGTTTCCGGTTTAAACACCTCTTCCTGTGTGGCTCACTTGTTTTC  
CATGTTGGTGATGAGTGGCTAGAATTTCTTCTATCCACAGCTGAAGCCATGGGTTCACTAT  
ATCCCAGTCAAAACAGATCTCTCCAATGTCCAAGAGCTGTTACAATTTGTAAAAGCAAAT  
GATGATGTAGCTCAAGAGATTGCTGAAAGGGGAAGCCAGTTTATTAGGAACCATTTCAG  
ATGGATGACATCACCTGTTACTGGGAGAACCTCTTGAGTGAATACTCTAAATTCCTGTCT  
TATAATGTAACGAGAAGGAAAGGTTATGATCAAATTATTTCCCAAATGTTGAAAACCTGAA  
CTATAGTAGTCATCATAGGACCATAGTCCTCTTTGTGGCAACAGATCTCAGATATCCTAC  
GGTGAGAAGCTTACCATAAGCTTGGCTCCTATACCTTGAATATCTGCTATCAAGCCAAAT  
ACCTGGTTTTTCTTATCATGCTGCACCCAGAGCAACTCTTGAGAAAGATTTAAAATGTGT  
CTAATACTGATATGAAGCAGTTCAACTTTTTGGATGAATAAGGACCAGAAATCGTGAG  
ATGTGGATTTTGAACCAACTCTACCTTTTCATTTTCTTAAGACCAATCACAGCTTGTGCC  
TCAGATCATCCACCTGTGTGAGTCCATCACTGTGAAATTGACTGTGTCCATGTGATGATG  
CCCTTTGTCCCATTTATTTGGAGCAGAAAATTCGTCAATTTGGAAGTAGTACAACCTCATTGC  
TGGAATTGTGAAATTATTCAAGGCGTGATCTCTGTCACTTTATTTTAAATGTAGGAAACCC  
TATGGGGTTTATGAAAAATACTTGGGGATCATTCTCTGAATGGTCTAAGGAAGCGGTAGC  
CATGCCATGCAATGATGTAGGAGTTCTCTTTTGTAAAACCATAAACTCTGTTACTCAGGA  
GGTTTCTATAATGCCACATAGAAAGAGGCCAATTGCATGAGTAATTATTGCAATTGGATT  
TCAGGTTCCCTTTTTGTGCCTTCATGCCCTACTTCTTAATGCCTCTCTAAAGCCAAA



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**FIGURE 136**

MEWWASSPLRLWLLLFLLP  
SAQGRQKESGSKWKVFI  
DQINRSLNYP  
CSCSYHGV  
I  
EEDLTPFRGGISRK  
MMAEVVRRKLGTHYQIT  
KNRLYREND  
CMFPSRC  
SGVEHFI  
LEVIG  
RLPDMEMVINVRDYPQVP  
KWM  
EPAIPVFSFSKTSEYH  
DIMYP  
AWTFWEGGPAVWPIYPTG  
LGRWDLFREDLVR  
SAAQWPWKKKNSTAYFRG  
SRTSPERDPLILL  
SRKNPKLVDAEYTKNQ  
AWKSMKDTLGKPA  
AKDVHLVDHCKYKYLE  
FNFRGVAASFRFKHL  
FLCGSLVFHVGDEWLEF  
FYPQLKPWVHYIPV  
KTDLSNVQELLQFVK  
ANDDVAQEIAERGSQ  
FIRNHLQMD  
DITCYWE  
NLLSEYSKFLSYNV  
TRRKG  
YDQIIPKMLKTEL

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**FIGURE 137**

ATTCTCCTAGAGCATCTTTGGAAGCATGAGGCCACGATGCTGCATCTTGGCTCTTGTCTG  
CTGGATAACAGTCTTCCTCCTCCAGTGTTCAAAGGAACTACAGACGCTCCTGTTGGCTC  
AGGACTGTGGCTGTGCCAGCCGACACCCAGGTGTGGGAACAAGATCTACAACCCTTCAGA  
GCAGTGCTGTTATGATGATGCCATCTTATCCTTAAAGGAGACCCGCCGCTGTGGCTCCAC  
CTGCACCTTCTGGCCCTGCTTTGAGCTCTGCTGTCCCGAGTCTTTTGGCCCCCAGCAGAA  
GTTTCTTGTGAAGTTGAGGGTTCTGGGTATGAAGTCTCAGTGTCACCTTATCTCCCATCTC  
CCGGAGCTGTACCAGGAACAGGAGGCACGTCCTGTACCCATAAAAAACCCAGGCTCCACT  
GGCAGACGGCAGACAAGGGGAGAAGAGACGAAGCAGCTGGACATCGGAGACTACAGTTGA  
ACTTCGGAGAGAAGCAACTTGACTTCAGAGGGATGGCTCAATGACATAGCTTTGGAGAGG  
AGCCAGCTGGGGATGGCCAGACTTCAGGGGAAGAATGCCTTCCTGCTTCATCCCCTTTC  
CAGCTCCCCCTCCCGCTGAGAGCCACTTTCATCGGCAATAAAATCCCCCACATTTACCATCT

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## FIGURE 138

MRPRCCILALVCWITVFLQCSKGTDDAPVGSGLWLCQPTPRCGNKIYNPSEQCCYDDAI  
LSLKETRRCGSTCTFWPCFELCCPESFGPQQKFLVKLRVLGMKSQCHLSPIRSCTRNRR  
HVLYP

**Important features:**

**Signal sequence:**

amino acids 1-21

**N-myristoylation sites:**

amino acids 33-39, 70-76

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**FIGURE 139**

CCTCTGTCCACTGCTTTTCGTGAAGACAAGATGAAGTTCACAATTGTCTTTGCTGGACTTC  
TTGGAGTCTTTCTAGCTCCTGCCCTAGCTAACTATAATATCAACGTCAATGATGACAACA  
ACAATGCTGGAAGTGGGCAGCAGTCAGTGAGTGTCAACAATGAACACAATGTGGCCAATG  
TTGACAATAACAACGGATGGGACTCCTGGAATTCCATCTGGGATTATGGAAATGGCTTTG  
CTGCAACCAGACTCTTTCAAAAGAAGACATGCATTGTGCACAAAATGAACAAGGAAGTCA  
TGCCCTCCATTCAATCCCTTGATGCACTGGTCAAGGAAAAGAAGCTTCAGGGTAAGGGAC  
CAGGAGGACCACCTCCCAAGGGCCTGATGTACTCAGTCAACCCAAACAAAGTCGATGACC  
TGAGCAAGTTCGGAAAAAACATTGCAAACATGTGTTCGTGGGATTCCAACATACATGGCTG  
AGGAGATGCAAGAGGCAAGCCTGTTTTTTTACTCAGGAACGTGCTACACGACCAGTGTAC  
TATGGATTGTGGACATTTCTTCTGTGGAGACACGGTGGAGAACTAAACAATTTTTTAAA  
GCCACTATGGATTTAGTCATCTGAATATGCTGTGCAGAAAAAATATGGGCTCCAGTGGTT  
TTTACCATGTCATTCTGAAATTTTCTCTACTAGTTATGTTTGATTTCTTTAAGTTTCAA  
TAAATCATTTAGCATTGAAAAAA

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**FIGURE 140**

MKFTIVFAGLLGVFLAPALANYNINVNDDNNNAGSGQQSVSVNNEHNVANVDNNNGWDSW  
NSIWDYGNNGFAATRLFQKKTCTIVHKMNKEVMPSIQSLDALVKEKKLQKGPGGPPPKGLM  
YSVNPKNKVDDLKFGKNIANMCRGIPTYMAEEMQEASLFFYSGTCYTTSVLWIVDISFCG  
DTVEN

**Signal Peptide:**  
amino acids 1-20

**N-myristoylation Sites:**  
amino acids 67-72, 118-123, 163-168

**Flavodoxin protein homology:**  
amino acids 156-174

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**FIGURE 141**

GGTCCTTAATGGCAGCAGCCGCCGCTACCAAGATCCTTCTGTGCCTCCCGCTTCTGCTCC  
TGCTGTCCGGCTGGTCCCGGGCTGGGCGAGCCGACCCTCACTCTCTTTGCTATGACATCA  
CCGTCAATCCCTAAGTTCAGACCTGGACCACGGTGGTGTGCGGTTCAAGGCCAGGTGGATG  
AAAAGACTTTTCTTCACTATGACTGTGGCAACAAGACAGTCACACCTGTCAGTCCCCTGG  
GGAAGAACTAAATGTCAACGGCCTGGAAAGCACAGAACCCAGTACTGAGAGAGGTGG  
TGGACATACTTACAGAGCAACTGCGTGACATTCAGCTGGAGAATTACACACCCAAGGAAC  
CCCTCACCCCTGCAGGCAAGGATGTCTTGTGAGCAGAAAGCTGAAGGACACAGCAGTGGAT  
CTTGGCAGTTCAGTTTCGATGGGCAGATCTTCCTCCTCTTTGACTCAGAGAAGAGAATGT  
GGACAACGGTTCATCCTGGAGCCAGAAAGATGAAAGAAAAGTGGGAGAATGACAAGGTTG  
TGGCCATGTCCTTCCATTACTTCTCAATGGGAGACTGTATAGGATGGCTTGAGGACTTCT  
TGATGGGCATGGACAGCACCCTGGAGCCAAGTGCAGGAGCACCCTCGCCATGTCCTCAG  
GCACAACCCAACCTCAGGGCCACAGCCACCACCCTCATCCTTTGCTGCCTCCTCATCATCC  
TCCCCTGCTTCATCCTCCCTGGCATCTGAGGAGAGTCTTTAGAGTGACAGGTTAAAGCT  
GATACCAAAAGGCTCCTGTGAGCACGGTCTTGATCAAACCTCGCCCTTCTGTCTGGCCAGC  
TGCCACAGACCTACGGTGTATGTCCAGTGGCCTCCAGCAGATCATGATGACATCATGGAC  
CCAATAGCTCATTCAGTGCCTTGATTCTTTTGCCAACAATTTTACCAGCAGTTATACCT  
AACATATTATGCAATTTTCTTGGTGCTACCTGATGGAATTCCTGCACTTAAAGTTCTG  
GCTGACTAAACAAGATATATCATTTTCTTTCTTCTCTTTTGTGTTGGAAAATCAAGTACT  
TCTTTGAATGATGATCTCTTTCTTGCAAATGATATTGTCAGTAAAATAATCACGTTAGAC  
TTCAGACCTCTGGGGATTCTTTCCGTGTCCTGAAAGAGAATTTTAAATTATTTAATAAG  
AAAAAATTTATATTAATGATTGTTTCTTTAGTAATTTATTGTTCTGTACTGATATTTAA  
ATAAGAGTTCTATTTCCCAAAAAAAAAAAAAAAAAAAAAA

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**FIGURE 142**

MAAAAATKILLCLPLLLLLSGWSRAGRADPHSLCYDITVIPKFRPGPRWCAVQGQVDEKT  
FLHYDCGNKTVTPVSP LGKKLNVT TAWKAQNPVLREVVDILTEQLRDIQLENYTPKEPLT  
LQARMSCEQKAEGHSSGSWQFSFDGQIFLLFDSEKRMWTTVHPGARKMKEKWENDKVVAM  
SFHYFSMGDCIGWLEDFLMGMDSTLEPSAGAPLAMSSGTTQLRATATTLILCCLLIILPC  
FILPGI

**Important features:****Signal peptide:**

amino acids 1-25

**Transmembrane domain:**

amino acids 224-246

**N-glycosylation site:**

amino acids 68-72, 82-86

**N-myristoylation site:**

amino acids 200-206, 210-216

**Amidation site:**

amino acids 77-81

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**FIGURE 143**

AATGTGAGAGGGGCTGATGGAAGCTGATAGGCAGGACTGGAGTGTTAGCACCAGTACTGG  
ATGTGACAGCAGGCAGAGGAGCACCTTAGCAGCTTATTAGTGTCCGATTCTGATTCCGGC  
AAGGATCCAAGCATGGAATGCTGCCGTGCGGCAACTCCTGGCACACTGCTCCTCTTTCTG  
GCTTTCCTGCTCCTGAGTTCCAGGACCGCACGCTCCGAGGAGGACCGGGACGGCCTATGG  
GATGCCTGGGGCCCATGGAGTGAATGCTCACGCACCTGCGGGGGAGGGGCCTCCTACTCT  
CTGAGGCGCTGCCTGAGCAGCAAGAGCTGTGAAGGAAGAAATATCCGATACAGAACATGC  
AGTAATGTGGACTGCCACCAGAAGCAGGTGATTTCCGAGCTCAGCAATGCTCAGCTCAT  
AATGATGTCAAGCACCATGGCCAGTTTTATGAATGGCTTCCTGTGTCTAATGACCCTGAC  
AACCCATGTTCACTCAAGTGCCAAGCCAAAGGAACAACCCCTGGTTGTTGAACTAGCACCT  
AAGGTCTTAGATGGTACGCGTTGCTATACAGAATCTTTGGATATGTGCATCAGTGGTTTA  
TGCCAAATTGTTGGCTGCGATCACCAGCTGGGAAGCACCGTCAAGGAAGATAACTGTGGG  
GTCTGCAACGGAGATGGGTCCACCTGCCGGCTGGTCCGAGGGCAGTATAAATCCCAGCTC  
TCCGCAACCAAATCGGATGATACTGTGGTTGCACTTCCCTATGGAAGTAGACATATTCGC  
CTTGTCTTAAAGGTCTGATCACTTATATCTGGAACCAAAACCCTCCAGGGGACTAAA  
GGTGAACACAGTCTCAGCTCCACAGGAACCTTCTTGTGGACAATTCTAGTGTGGACTTC  
CAGAAATTTCCAGACAAAGAGATACTGAGAATGGCTGGACCACTCACAGCAGATTTTATT  
GTCAAGATTTCGTAACCTCGGGCTCCGCTGACAGTACAGTCCAGTTCATCTTCTATCAACCC  
ATCATCCACCGATGGAGGGAGACGGATTTCTTTCCTTGCTCAGCAACCTGTGGAGGAGGT  
TATCAGCTGACATCGGCTGAGTGCTACGATCTGAGGAGCAACCGTGTGGTTGCTGACCAA  
TACTGTCACTATTACCCAGAGAACATCAAACCCAAACCCAAGCTTCAGGAGTGCAACTTG  
GATCCTTGTCCAGCCAGTGACGGATACAAGCAGATCATGCCTTATGACCTCTACCATCCC  
CTTCTCGGTGGGAGGCCACCCCATGGACCGGTGCTCCTCCTCGTGTGGGGGGGGCATC  
CAGAGCCGGGCAGTTTTCTGTGTGGAGGAGGACATCCAGGGGCATGTCACTTCAGTGGAA  
GAGTGGAATGCATGTACACCCCTAAGATGCCCATCGCGCAGCCCTGCAACATTTTTTGAC  
TGCCCTAAATGGCTGGCACAGGAGTGGTCTCCGTGCACAGTGACATGTGGCCAGGGCCTC  
AGATACCGTGTGGTCTCTGCATCGACCATCGAGGAATGCACACAGGAGGCTGTAGCCCA  
AAAACAAAGCCCCACATAAAAGAGGAATGCATCGTACCCACTCCCTGCTATAAACCCAAA  
GAGAACTTCCAGTCGAGGCCAAGTTGCCATGGTTCAAACAAGCTCAAGAGCTAGAAGAA  
GGAGCTGCTGTGTGAGAGGAGCCCTCGTAAAGTTGTAAAAGCACAGACTGTTCTATATTTG  
AAACTGTTTTGTTTAAAGAAAGCAGTGTCTCACTGGTTGTAGCTTTCATGGGTTCTGAAC  
TAAGTGTAATCATCTCACCAAGCTTTTTGGCTCTCAAATTAAGATTGATTAGTTTTCAA  
AAAAAAAA



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**FIGURE 144**

MECCRRATPGTLLLFLAFLLLSSRTARSEEDRDGLWDAGPWSECSRTC GGGASYSLRRC  
LSSKSCEGRNIRYRTCSNVDCPPEAGDFRAQQCSAHNDVKHHGQFYEWLPVSNDPDNPCS  
LKCQAKGTTLVVELAPKVLDTGTRCYTESLDMCISGLCQIVGCDHQLGSTVKEDNCGVCNG  
DGSTCRLVRGQYKSQLSATKSDDTVVALPYGSRHIRLVKGPDLHLYLETKTLQGTKGENS  
LSSTGTFLVDNSSVDFQKFPDKEILRMAGPLTADFIVKIRNSGSADSTVQFIFYQPIIHR  
WRETDFFPSCSATCGGGYQLTSAECYDLRSNRVVADQYCHYYPENIKPKPKLQECNLDPCP  
ASDGYKQIMPYDLYHPLPRWEATPWTACSSSCGGGIQSRAVSCVEEDIQGHVTSVEEWKC  
MYTPKMPIAQPCNIFDCPKWLAQEWSPCTVTGQGLRYRVVLCIDHRGMHTGGCSPKTKP  
HIKEECIVPTPCYKPKKEKL PVEAKLPWFKQAQEELEEGA AVSEEPS

**Important features:**

**Signal peptide:**

amino acids 1-25

**N-glycosylation site:**

amino acids 251-254

**Thrombospondin 1:**

amino acids 385-399

**von Willebrand factor type C domain proteins:**

amino acids 385-399, 445-459 and 42-56

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**FIGURE 145**

GGAGGAGGGAGGGCGGGCAGGCGCCAGCCCAGAGCAGCCCCGGGCACCAGCACGGACTCT  
CTCTTCCAGCCCAGGTGCCCCCACTCTCGCTCCATTTCGGCGGGAGCACCCAGTCCTGTA  
CGCCAAGGAACTGGTCTCTGGGGGCACCAATGGTTTTCGGCGGCAGCCCCAGCCTCCTCATC  
CTTCTGTTGCTGCTGCTGCGGGTCTGTGCCTGCTACCGACGCCCCGCTCTGTGCCCCCTGAAG  
GCCACGTTCTTGAGGATGTGGCGGGTAGTGGGGAGGCCGAGGGCTCGTCGGCCTCCTCC  
CCGAGCCTCCCGCCACCCTGGACCCCGGCCCTCAGCCCCACATCGATGGGGCCCCAGCCC  
ACAACCCTGGGGGGCCCATCACCCCCACCAACTTCCTGGATGGGATAGTGGACTTCTTC  
CGCCAGTACGTGATGCTGATTGCTGTGGTGGGCTCCCTGGCCTTTCTGCTGATGTTTCATC  
GTCTGTGCCGCGGTTCATCACCCGGCAGAAGCAGAAGGCCTCGGCCTATTACCCATCGTCC  
TTCCCCAAGAAGAAGTACGTGGACCAGAGTGACCGGGCCGGGGGCCCCCGGGCCTTCAGT  
GAGGTCCCCGACAGAGCCCCCGACAGCAGGCCCGAGGAAGCCCTGGATTCTCCCGGCAG  
CTCCAGGCCGACATCTTGCGCCGCCACCCAGAACCTCAAGTCCCCCACCAGGGCTGCACTG  
GGCGGTGGGGACGGAGCCAGGATGGTGGAGGGCAGGGGCGCAGAGGAAGAGGAGAAGGGC  
AGCCAGGAGGGGGACCAAGGAGTCCAGGGACATGGGGTCCCAGTGGAGACACCAGAGGCG  
CAGGAGGAGCCGTGCTCAGGGGTCTTGGAGGGGCTGTGGTGGCCGGTGAGGGCCAAGGG  
GAGCTGGAAGGGTCTCTCTTGTTAGCCAGGAAGCCAGGGACCAGTGGGTCCCCCGAA  
AGCCCCTGTGCTTGCAGCAGTGTCCACCCAGTGTCTAACAGTCTCCCGGGCTGCCAGC  
CCTGACTGTGCGGGCCCCCAAGTGGTCACCTCCCCGTGTATGAAAAGGCCTTCAGCCCTGA  
CTGCTTCCTGACACTCCCTCCTTGGCCTCCCTGTGGTGCCAATCCCAGCATGTGCTGATT  
CTACAGCAGGCAGAAATGCTGGTCCCCGGTGCCCCGGAGGAATCTTACCAAGTGCCATCA  
TCCTTCACCTCAGCAGCCCCAAAGGGCTACATCCTACAGCACAGCTCCCCTGACAAAGTG  
AGGGAGGGCACGTGTCCCTGTGACAGCCAGGATAAAACATCCCCCAAAGTGCTGGGATTA  
CAGGCGTGAGCCACCGTGCCCCGGCCCCAACTACTTTTTTAAACAGCTACAGGGTAAATC  
CTGCAGCACCCACTCTGGAAAATACTGCTCTTAATTTTCTGAAGGTGGCCCCCTGTTTC  
TAGTTGGTCCAGGATTAGGGATGTGGGGTATAGGGCATTTAAATCCTCTCAAGCGCTCTC  
CAAGCACCCCCGGCCTGGGGGTGAGTTTCTCATCCCGCTACTGCTGCTGGGATCAGGTTG  
AATGAATGGAATCTTCCTGTCTGGCCTCCAAAGCAGCCTAGAAGCTGAGGGGCTGTGTT  
TGAGGGGACCTCCACCCTGGGGAAGTCCGAGGGGCTGGGGAAGGGTTTCTGACGCCCAGC  
CTGGAGCAGGGGGGCCCTGGCCACCCCCTGTTGCTCACACATTGTCTGGCAGCCTGTGTC  
CACAATATTTCGTCAGTCCTCGACAGGGAGCCTGGGCTCCGTCTCTTTAGGGAGGCTCT  
GGCAGGAGGTCTCTCCCCCATCCCTCCATCTGGGGCTCCCCCAACCTCTGCACAGCTCT  
CCAGGTGCTGAGATATAATGCACCAGCACATAAACCTTTATTCCGGCCTGAAAAAAAAA  
AAGA

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**FIGURE 146**

MVSAAAPSLILLILLLLGSPATDARSVPLKATFLEDVAGSGEAEAGSSASSPSLPPPWTP  
ALSPTSMGPQPTTLGGSPPTNFLDGIVDFFRQYVMLIAVVGSLAFLLMFIVCAAVITRQ  
KQKASAYYPSSFPPKKKYVDQSDRAGGPRAFSEVPDRAPDSRPEEALDSSRQLQADILAAT  
QNLKSPTRAALGGGDGARMVEGRGAEEEEKGSQEGDQEVQGHGVPVETPEAQEEPCSGVL  
EGAVVAGEGQGELEGSLLLAQEAQGPVGPPEPCACSSVHPSV

**Signal peptide:**  
amino acids 1-25

**Transmembrane domain:**  
amino acids 94-118

**N-myristoylation site:**  
amino acids 18-24, 40-46, 46-52, 145-151, 192-198, 193-199,  
211-217, 238-244, 242-248

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**FIGURE 147**

GAAAGACGTGGTCCTGACAGACAGACAATCCTATTCCCTACCAAAATGAAGATGCTGCTG  
CTGCTGTGTTTGGGACTGACCCCTAGTCTGTGTCCATGCAGAAGAAGCTAGTTCTACGGGA  
AGGAACTTTAATGTAGAAAAGATTAATGGGGAATGGCATACTATTATCCTGGCCTCTGAC  
AAAAGAGAAAAGATAGAAGAACATGGCAACTTTAGACTTTTTCTGGAGCAAATCCATGTC  
TTGGAGAATTCCTTAGTTCTTAAAGTCCATACTGTAAGAGATGAAGAGTGCTCCGAATTA  
TCTATGGTTGCTGACAAAACAGAAAAGGCTGGTGAATATTCTGTGACGTATGATGGATTC  
AATACATTTACTATACCTAAGACAGACTATGATAACTTTCTTATGGCTCACCTCATTAAAC  
GAAAAGGATGGGGAAACCTTCCAGCTGATGGGGCTCTATGGCCGAGAACCAGATTTGAGT  
TCAGACATCAAGGAAAGGTTTGCACAACATATGTGAGGAGCATGGAATCCTTAGAGAAAAT  
ATCATTGACCTATCCAATGCCAATCGCTGCCCTCAGGCCCGAGAATGAAGAATGGCCTGA  
GCCTCCAGTGTTGAGTGGACACTTCTCACCAGGACTCCACCATCATCCCTTCCTATCCAT  
ACAGCATCCCCAGTATAAATTCTGTGATCTGCATTCCATCCTGTCTCACTGAGAAGTCCA  
ATTCCAGTCTATCAACATGTTACCTAGGATACCTCATCAAGAATCAAAGACTTCTTTAAA  
TTTCTCTTTGATACACCCTTGACAATTTTTCATGAAATTATTCCTCTTCCTGTTCAATAA  
ATGATTACCCTTGCACTTAA

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## FIGURE 148

MKMLLLCLGLTLVCVHAEEASSTGRNFNVEKINGEWHTIILASDKREKIEEHGNFRLFL  
EQIHVLENSLVLVHTVRDEECSELSMVADKTEKAGEYSVTYDGFNTFTIPKTDYDNFLM  
AHLINERKDGETFQLMGLYGREPDLSSEIKERFAQLCEEHGILRENIIDLSNANRCLQARE



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**FIGURE 150**

MKFQGPLACLLLLALCLGSGEAGPLQSGEESTGTNIGEALGHGLGDALSEGVGKAIGKEAG  
GAAGSKVSEALGQGTREAVGTGVRQVPGFGAADALGNRVGEAAHALGNTGHEIGRQAEDV  
IRHGADAVRGSWQGVPGHSGAWETSGGHGIFGSQGGGLGGQGQGNPGGLGTPWVHGYPGNS  
AGSFGMNPQGAPWGQGGNGGPPNFGTNTQGAVAQPGYGSVRASNQNEGCTNPPPSGSGGG  
SSNSGGSGSQSGSSSGSGSNGDNNNGSSSGSSSGSSSGSSSGSSSGSSSGSSGSSGSSGNSGGS  
RGDSGSESSWGSSTGSSSGNHGSGGGNGHKPGCEKPGNEARGSGESGIQGRGQGVSSN  
MREISKEGNRLLGGSGDNYRGQSSWGSGGGDAVGGVNTVNSETPGMFNFDTFWKNFKS  
KLGFINWDAINKDQRSSRIP

**Signal peptide:**  
amino acids 1-21

**N-glycosylation site:**  
amino acids 265-269

**Glycosaminoglycan attachment site:**  
amino acids 235-239, 237-241, 244-248, 255-259, 324-328,  
388-392

**Casein kinase II phosphorylation site:**  
amino acids 26-30, 109-113, 259-263, 300-304, 304-308

**N-myristoylation site:**  
amino acids 17-23, 32-38, 42-48, 50-56, 60-66, 61-67, 64-70,  
74-80, 90-96, 96-102, 130-136, 140-146, 149-155, 152-158,  
155-161, 159-165, 163-169, 178-184, 190-196, 194-200,  
199-205, 218-224, 236-242, 238-244, 239-245, 240-246,  
245-251, 246-252, 249-252, 253-259, 256-262, 266-272,  
270-276, 271-277, 275-281, 279-285, 283-289, 284-290,  
287-293, 288-294, 291-297, 292-298, 295-301, 298-304,  
305-311, 311-317, 315-321, 319-325, 322-328, 323-329,  
325-331, 343-349, 354-360, 356-362, 374-380, 381-387,  
383-389, 387-393, 389-395, 395-401

**Cell attachment sequence:**  
amino acids 301-304

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**FIGURE 151**

CGGCCACAGCTGGCATGCTCTGCCTGATCGCCATCCTGCTGTATGTCCTCGTCCAGTACC  
TCGTGAACCCCGGGGTGCTCCGCACGGACCCAGATGTCAAGAATATGAACACGTGGCTG  
CTGTTCCCTCCCCCTGTTCCCGGTGCAGGTGCAGACCCTGATAGTCGTGATCATCGGGATG  
CTCGTGCTCCTGCTGGACTTTCTTGGCTTGGTGCACCTGGGCCAGCTGCTCATCTTCAC  
ATCTACCTGAGTATGTCCCCACCCTAAGCCCCCGATCCCCCAAGGCTGGGTGGTCAGA  
GCTGCTCATCTTACACCTCTACTTGAGTATGTCCCTAACCTGAGCCCCCACGCCTGGG  
GCCAGAGTCTTTGTCCCCGTGTGCGCATGTGTTTCAGGGTCAGCCTCTCCAGAAGTGAG  
ATCATGGACAAAAAGGGCAAATCACAGGAAGAAATTAAATCCATGAGGACCCAGCAGGCC  
CAGCAAGAAGCTGAACTCACGCCGAGACCTGCAGGAGTGGTGCCAGGTGCTTGAAGTAAC  
AAGTTTAAATGTTTCAAGAGACAATGGAATGGAATCTATTAGGCAAGAACAGGACATTATG  
AAATAAGGACAGGTGGACTTCCAAAAACACAAGTAGAAATTCTAACAATGAAATATATTA  
CAGGCAGGTACCCACTAACCAACAACCTGAAGCGAGAGCTGTGGTCTTGCTTGGTCTCA  
CAGTGGGCACAGCGGTAGGCGGTCAAGTCATGTTGCTGAACGACGGAGGGTAAACTCCCCA  
GCCCCAAGAAAACCTGTGTTGGAAGTAACAACAACCTCCCTGCTCCTGGCACCAGCCGTT  
TTGGTCATGGTGGGCCAGCTGCAAAGCGTCTTCCATTCTCTGGGCAGTGGTGGCCCCGAG  
GCTGTGGCCTCTCAGGGGGTTTCTGTGGACACGGGCAGCAGAGTGTGTCCAGGCCAGCCC  
CCAAGAATGCCCTGCTCCTGACAGCTTGGCCAACCCCTGGTCAGGGCAGAGGGAGTTGGG  
TGGGTCAGGCTCTGGGCTCACCTCCATCTCCAGAGCATCCCCTGCCTGCAGTTGTGGCAA  
GAACGCCCAGCTCAGAATGAACACACCCACCAAGAGCCTCCTTGTTTATAACACAGGT  
TACCCTACAAACCACTGTCCCCACACAACCTGGGGATGTTTTAAACACACACCTCTAA  
CGCATATCTTACAGTCACTGTTGTCTTGCCTGAGGGTTGAATTTTTTTTAAATGAAAGTGC  
AATGAAAATCACTGGATTAAATCCTACGGACACAGAGCTGAAAAAAAAAAAAAAAAAAAA  
AAAAAAAAAAAA



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## FIGURE 152

MNTWLLFLPLFPVQVQTLIVVIIGMLVLLLDLGLVHLGQLLIFHIYLSMSPTLSPRSPQ  
GWVVRAAHLTPLLEYVPNPEPPTPGARVFVPRVRMCSGSASPRSEIMDKKGKSQEEIKSM  
RTQQAQQEAEELTPRPAGVPGA

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**FIGURE 153**

AACTGGAAGGAAAGAAAGAAAGGTCAGCTTTGGCCCAGATGTGGTTACCCCTTGGTCTCC  
TGTCTTTATGTCTTTCTCCTCTTCCTATTCTGTTCATCTCCCTCACTTAAGTCTCAGGCCT  
GTCAGCAGCTCCTGTGGACATTGCCATCCCCCTCTGGTAGCCTTCAGAGCAAACAGGACAA  
CCTATGTTATGGATGTTTCCACCAACCAGGGTAGTGGCATGGAGCACCGTAACCATCTGT  
GCTTCTGTGATCTCTATGACAGAGCCACTTCTCCACCTCTGAAATGTTCCCTGCTCTGAA  
ATCTGGCATGAGATGGCACAGGTGACCACGCAGAAGCCACCAGAATCTTGCCTGCCCTAT  
TCCTCCTCCCAAGTCTGTTCTCTTATTGTCAACCTCAGCACAAACAGGCTGGCGCCAATGG  
CATTACAGAGAAAGCAATCTGTGTGGCTAGTGGGCAGATTACCATGCAAGCCCCAGGAGA  
AATGGAGGAGCTTTGTAGCCACCTCCCTGTCAGCCAGTATTAACATGTCCCCTTCCCCCT  
GCCCCGCCGTAGATTCAAGGACATTGCCCCCTGTGTGCCACCAAACCAGGACTTTCCCCTT  
GGCTTGGCATCCCTGGCTCTCTCCTGGTACCCAGCAAGACGTCTGTTCCAGGGCAGTGTA  
GCATCTTTCAAGCTCCGTTACTATGGCGATGGCCATGATGTTACAATCCCACCTTGCCTGA  
ATAATCAAGTGGGAAGGGGAAGCAGAGGGAAATGGGGCCATGTGAATGCAGCTGCTCTGT  
TCTCCCTACCCTGAGGAAAAACCAAAGGGAAGCAACAGGAACCTTCTGCAACTGGTTTTTA  
TCGGAAAGATCATCCTGCCTGCAGATGCTGTTGAAGGGGCACAAGAAATGTAGCTGGAGA  
AGATTGATGAAAGTGCAGGTGTGTAAGGAAATAGAACAGTCTGCTGGGAGTCAGACCTGG  
AATTCTGATTCCAAACTCTTTATTACTTTGGGAAGTCACTCAGCCTCCCCGTAGCCATCT  
CCAGGGTGACGGAACCCAGTGTATTACCTGCTGGAACCAAGGAAACTAACAATGTAGGTT  
ACTAGTGAATACCCCAATGGTTTCTCCAATTATGCCCATGCCACCAAAACAATAAAACAA  
AATTCTCTAACACTGAAA

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## FIGURE 154

MWLPLGLLSLCLSPILSSPSLKSQACQQLLWTLPSPLVAFRANRTTYVMDVSTNQSG  
MEHRNHLCFCDLYDRATSPPLKCSLL

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**FIGURE 155**

GTAGCGCGTCTTGGGTCTCCCGGCTGCCGCTGCTGCCGCCGCCGCTCGGGTCGTGGAGC  
CAGGAGCGACGTACCGCCATGGCAGGCATCAAAGCTTTGATTAGTTTGTCTTTGGAGG  
AGCAATCGGACTGATGTTTTTTGATGCTTGGATGTGCCCTTCCAATATACAACAAATACTG  
GCCCCCTCTTTGTTCTATTTTTTTACATCCTTTCACCTATTCCATACTGCATAGCAAGAAG  
ATTAGTGGATGATACAGATGCTATGAGTAACGCTTGTAAGGAACTTGCCATCTTTCTTAC  
AACGGGCATTGTCGTGTCAGCTTTTGGACTCCCTATTGTATTTGCCAGAGCACATCTGAT  
TGAGTGGGGAGCTTGTGCACTTGTTCTCACAGGAAACACAGTCATCTTTGCAACTATACT  
AGGCTTTTTCTTGGTCTTTGGAAGCAATGACGACTTCAGCTGGCAGCAGTGGTGA AAAAGA  
AATTACTGAACTATTGTCAAATGGACTTCCTGTCAATTTGTTGGCCATTACGCACACAGG  
AGATGGGGCAGTTAATGCTGAATGGTATAGCAAGCCTCTTGGGGGTATTTTAGGTGCTCC  
CTTCTCACTTTTATTGTAAGCATACTATTTTCACAGAGACTTGCTGAAGGATTA AAAGGA  
TTTTCTCTTTTGGAAAAGCTTGACTGATTTACACTTATCTATAGTATGCTTTTTTGTGGT  
GTCCTGCTGAATTTAAATATTTATGTGTTTTTCTGTTAGGTTGATTTTTTTTGGAAATCA  
ATATGCAATGTTAAACACTTTTTTAATGTAATCATTTGCATTGGTTAGGAATTCAGAATT  
CCGCCGCTCTATTACTGGTCAAGTACATCTTTTCTCTTAAATTTATTTAGCCTCCATTA  
TTACAAAAAATTATAAAAAATAAGTTTTTCAGTCAGTCAGGATGACATCACTCCCAATGTTA  
TGCAGACATACAGACGGTTGGCATACTGTTATAGACTGTATACTCAGTGCAAAATATAGCTG  
CATTTATACCTCAGAGGGGCCAAGTGTTAATGCCCATGCCCTCCGTAAAGGGTTGTTGGT  
TTTACTGGTAGACAGATGTTTTGTGGATTGAAAATTATTTTATGGAATTGCTACAGAGGA  
GTGCTTTTCTTCTCAATTGTTAGAAGAATTTATGTTAACTTTAAGGTAAGGGTGTA AAA  
ACATTTTGTAGATAAGGTTTTTATTTATGTTTATTATTGTTAGAGTGAGTTGCAATGTGG  
GAAGAAATGACATTGAAATTCAGTTTTTGAATCCTGTTTCTATTTATAAGTGAAATTTG  
TGATCTCCTATCAACCTTTCATGTTTTACCCTGTTAAATGGACATACATGGAACCACTA  
CTGATGAGGGACAGTTGTATGTTTGCATCATATATGCCAGAAAACCTTCCTCTGCTTCCT  
CTTTTTGACTTATTTGGTATGTTGTATATATTACATAAAATAACTTTTCAAATATAGTTT  
AATAACACTTAGAAGTGTTTACTTACCTGGAAAATAATTGCTATGCCGTACATTCAGAGT  
GCCCCCTCCCCTGCAAGGCCTTGCCATGATTAAACAAGTAACTTGTTAGTCTTACAGATAA  
TTCATGCATTAAACAGTTTAAAGATTTAGACCATGGTAATAGTAGTTCTTATTCTCTAAGGT  
TATATCATATGTAATTTAAAGTATTTTTAAGACAAGTTTCCTGTATACCTCTGAACTGT  
TTTGATTTTGTAGTTCATCATGATAGATCTGCTGTTTCCTTATAAAAGGCATTTGTTGTGT  
GAGTTAATGCAAAGTAGCCAAGTCCAGCTATATAGCAGCTTCAGAAACATACCTGACCAA  
AAAATTTCCAGTAACCAAGGCATGATCAATTTATAGTGGTCGTTTACATCTAATAATTATC  
AGGACTTTTTTTCAGGAGTGGGTTATAAAAACATTCAGTTGGTCTGACAGTATTTTGTTA  
AGGATATTTGTTTGTATGTTTATTTCAGTATACTTACATAAAAATTATTTGCCATCAGCC  
AAAACCTCAGTAATCATGACAGCTGTCTGTTGTTTATGAAGTTTATTTCTCAAGAAAATG  
GGAATAAATTTGGGATTTGTTTCAGCTTTTTTACTAAAGATGCCTAAAGCCACAGGTTTTA  
TTGCCCTAACTTAAGCCATGACTTTTAGATATGAGATGACGGGAAGCAGGACGAAATATCG  
GCGTGTGGCTGGAGCCTTCCCCTGGAGGCTGAAAGTGGCTTGTGGTATTATAATGTTCA  
GATTTCAAGAGGAAGGTGCAGGTACACATGAGTTAGAGAGCTGGTGAGACAGTTGGGAAC  
TCTTTGTGCTTGTGATCTACTGGACTTTTTTTTTTGCAGGAAGTGCATTCTCTGGTCCTTC  
CCTATTTTCTGTTCTGGATGTCAGTGCAGTGCAGTGCCTACTGTTTTATCCACTTGGCCAC  
AGACTTTTTCTAACAGCTGCGTATTATTTCTATATACTAATTGCATTGGCAGCATTGTGT  
CTTTGACCTTGTATACTAGCTTGACATAGTGCTGTCTCTGATTTCTAGGCTAGTTACTTG  
AGATATGAATTTTCATAGAATATGCACTGATACAACATTACCATTCTTCTATGGAAAGA  
AACTTTTTGATGATGAAACAATAAAGATTTTAAATATCTATTTTAAAAA AAAAA

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## FIGURE 156

MAGIKALISLSFGGAIGLMFLMLGICALPIYNKYWPLFVLFFYILSPIPYCIARRLVDDTD  
AMSNACKELAIFLTGTGIVVSAFGLPIVFARAHLEWGACALVLTGNTVIFATILGFFLVF  
GSNDDFSWQQW

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## FIGURE 157

GTTTCTCATAGTTGGCGTCTTCTAAAGGAAAAACACTAAAATGAGGAACTCAGCGGACCG  
GGAGCGACGCAGCTTGAGGGAAGCATCCCTAGCTGTTGGCGCAGAGGGGCGAGGCTGAAG  
CCGAGTGGCCCCGAGGTGTCTGAGGGGCTGGGGCAAAGGTGAAAGAGTTTCAGAACAGCT  
TCCTGGAACCCATGACCCATGAAGTCTTGTGACATTTATACCGTCTGAGGGTAGCAGCT  
CGAAACTAGAAGAAGTGGAGTGTGCGCAGGACGGCAGTATCTCTTTGTGTGACCTGGC  
GGCCTATGGGACGTTGGCTTCAGACCTTTGTGATACACCATGCTGCGTGGGACGATGACG  
GCGTGGAGAGGAATGAGGCCTGAGGTCACTGGCTTGCCTCCTCCTAGCCACAGCAGGC  
TGCTTTGCTGACTTGAACGAGGTCCCTCAGGTCACCGTCCAGCCTGCGTCCACCGTCCAG  
AAGCCCGGAGGCACTGTGATCTTGGGCTGCGTGGTGGAACCTCCAAGGATGAATGTAACC  
TGGCGCCTGAATGGAAAGGAGCTGAATGGCTCGGATGATGCTCTGGGTGTCTCATCACC  
CACGGGACCTTCGTATCACTGCCCTTAACAACCACACTGTGGGACGGTACCAGTGTGTG  
GCCCCGATGCCTGCGGGGGCTGTGGCCAGCGTGCCAGCCACTGTGACACTAGCCAATCTC  
CAGGACTTCAAGTTAGATGTGCAGCACGTGATTGAAGTGGATGAGGGAAACACAGCAGTC  
ATTGCTTGCACCTGCCCTGAGAGCCACCCCAAAGCCAGGTCCGGTACAGCGTCAAACAA  
GAGTGGCTGGAGGCCTCCAGAGGTAACCTGATCATGCCCTCAGGGAACCTCCAGATT  
GTGAATGCCAGCCAGGAGGACGAGGGCATGTACAAGTGTGCAGCCTACAACCCAGTGACC  
CAGGAAGTGAAAACCTCCGGCTCCAGCGACAGGCTACGTGTGCGCCGCTCCACCGCTGAG  
GCTGCCCCGATCATCTACCCCCAGAGGCCCAAACCATCATCGTCACCAAAGGCCAGAGT  
CTCATTTCTGGAGTGTGTGGCCAGTGGAAATCCCACCCCCACGGGTACCTGGGCCAAGGAT  
GGGTCCAGTGTCACCGGCTACAACAAGACCGCTTCCCTGCTGAGCAACCTCCTCATCGAC  
ACCACCAGCGAGGAGGACTCAGGCACCTACCGCTGCATGGCCGACAATGGGGTTGGGCAG  
CCCGGGGCAGCGGTATCCTCTACAATGTCCAGGTGTTTGAACCCCCCTGAGGTACCATG  
GAGCTATCCCAGCTGGTATCCCCCTGGGGCCAGAGTGCCAAGCTTACCTGTGAGGTGCGT  
GGGAACCCCCGCCCTCCGTGCTGTGGCTGAGGAATGCTGTGCCCCCTCATCTCCAGCCAG  
CGCTCCGGCTCTCCCCGAGGGCCCTGCGCGTCTCAGCATGGGGCCTGAGGACGAAGGC  
GTCTACCAGTGATGGCCGAGAACGAGGTTGGGAGCGCCCATGCGGTAGTCCAGTGCCTG  
ACCTCCAGGCCAAGCATAACCCCAAGGCTATGGCAGGATGCTGAGCTGGCTACTGGCACA  
CCTCCTGTATCACCTCCAACTCGGCAACCCTGAGCAGATGCTGAGGGGGCAACCGGCG  
CTCCCCAGACCCCCAACGTCACTGGGGCCTGCTTCCCCGAAGTGTCCAGGAGAGAAGGGG  
CAGGGGGCTCCCGCCGAGGCTCCCATCATCTCAGCTCGCCCCGCACCTCCAAGACAGAC  
TCATATGAACTGGTGTGGCGGCCTCGGCATGAGGGCAGTGGCCGGGCGCCAATCCTCTAC  
TATGTGGTGAAACACCGCAAGCAGGTCAAAATTCCTCTGACGATTGGACCATCTCTGGC  
ATTCAGCCAAACAGCACCGCCTGACCCTCACAGACTTGACCCCGGAGCTTGTATGAA  
GTGGAGATGGCAGCTTAACTGTGCGGGAGAGGGCCAGACAGCCATGGTCACCTTCCGA  
ACTGGACGGCGCCCAAACCEGAGATCATGGCCAGCAAAGAGCAGAGATCCAGAGAGAC  
GACCCTGGAGCCAGTCCCCAGAGCAGCAGCCAGCCAGACCAGGCCGCTCTCCCCCCA  
GAAGCTCCCGACAGGCCACCATCTCCACGGCCTCCGAGACCTCAGTGATGCTGACCTGG  
ATTCCTCGTGGGAATGGTGGGTTCCTAATCCAGTCTTCCGTGTGGAGTACAAGAAGCTA  
AAGAAAGTGGGAGACTGGATTCTGGCCACCAGCGCCATCCCCCATCGCGGCTGTCCGTG  
GAGATCACGGGCCTAGAGAAAGGCACCTCCTACAAGTTTCGAGTCCGGGCTCTGAACATG  
CTGGGGGAGAGCGAGCCAGCGCCCCCTCTCGGCCCTACGTGGTGTGCGGGCTACAGCGGT  
CGCGTGTACGAGAGGCCCCGTGGCAGGTCTTTATATCACCTTCACGGATGCGGTCAATGAG  
ACCACCATCATGCTCAAGTGGATGTACATCCAGCAAGTAACAACAACACCCCAATCCAT  
GGCTTTTATATCTATTATCGACCCACAGACAGTGACAATGATAGTGACTACAAGAAGGAT  
ATGGTGAAGGGGACAAGTACTGGCACTCCATCAGCCACCTGCAGCCAGAGACCTCTTAC  
GACATTAAGATGCACTGCTTCAATGAAGGAGGGGAGAGCGAGTTGAGCAACCTGATGATC  
TGTGAGACCAAAGCTCGGAAGTCTTCTGGCCAGCCTGGTCTGACTGCCACCCCCAACTCTG  
GCCCCACACAGCCGCCCTTCTGAAACCATAGAGCGGCCGGTGGGCACTGGGGCCATG  
GTGGCTCGCTCCAGCGACCTGCCCTATCTGATTGTGCGGGTCTGCTGGGCTCCATCGTT  
CTCATCATCGTCACCTTCATCCCCCTTCTGCTTGTGGAGGGCCTGGTCTAAGCAAAACAT  
ACAACAGACCTGGGTTTTCTCGAAGTGCCCTTCCACCTCCTGCGCGTATACTATGGTG  
CCATTGGGAGGACTCCCAGGCCACCAGGCCAGTGGACAGCCCTACCTCAGTGGCATCAGT

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GGACGGGCCTGTGCTAATGGGATCCACATGAATAGGGGCTGCCCCTCGGCTGCAGTGGGC  
TACCCGGGCATGAAGCCCCAGCAGCACTGCCCAGGCGAGCTTCAGCAGCAGAGTGACACC  
AGCAGCCTGCTGAGGCAGACCCATCTTGGCAATGGATATGACCCCAAAGTCACCAGATC  
ACGAGGGGTCCCAAGTCTAGCCCGGACGAGGGCTCTTTCTTATACACACTGCCCGACGAC  
TCCACTCACCAGCTGCTGCAGCCCCATCACGACTGCTGCCAACGCCAGGAGCAGCCTGCT  
GCTGTGGGCCAGTCAGGGGTGAGGAGAGCCCCGACAGTCCTGTCTTGAAGCAGTGTGG  
GACCCTCCATTTCACTCAGGGCCCCCATGCTGCTTGGGCCTTGTGCCAGTTGAAGAGGTG  
GACAGTCCTGACTCCTGCCAAGTGAGTGGAGGAGACTGGTGTCCCCAGCACCCCGTAGGG  
GCCTACGTAGGACAGGAACCTGGAATGCAGCTCTCCCCGGGGCCACTGGTGCGTGTGTCT  
TTTGAACACCACCTCTCACAATTTAGGCAGAAGCTGATATCCAGAAAAGACTATATATT  
GTTTTTTTTTTAAAAAAAAGAGAAAAAGAGACAGAGAAAATTGGTATTTATTTTTC  
TATTATAGCCATATTTATATATTTATGCACTTGTAATAAATGTATATGTTTTATAATTC  
TGGAGAGACATAAGGAGTCCTACCCGTTGAGGTTGGAGAGGGAAAATAAAGAAGCTGCCA  
CCTAACAGGAGTCACCCAGGAAAGCACCGCACAGGCTGGCGCGGGACAGACTCCTAACCT  
GGGGCCTCTGCAGTGGCAGGCGAGGCTGCAGGAGGCCACAGATAAGCTGGCAAGAGGAA  
GGATCCCAGGCACATGGTTCATCACGAGCATGAGGGAACAGCAAGGGGCACGGTATCACA  
GCCTGGAGACACCCACACAGATGGCTGGATCCGGTGCTACGGGAAACATTTTCCTAAGAT  
GCCCATGAGAACAGACCAAGATGTGTACAGCACTATGAGCATTAATAAACCTTCCAGAAT  
CAATAATCCGTGGCAACATATCTCTGTAAAAACAAACACTGTAACCTCTAAATAAATGTT  
TAGTCTTCCCTGTAAAA

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**FIGURE 158**

MLRGTMTAWRGMREVTLACLLLATAGCFADLNEVPQVTVQPASTVQKPGGTIVILGCVVE  
PPRMNVTWRLNGKELNGSDDALGVLI THGTLVIT ALNNHTVGRYQCVARMPAGAVASVPA  
TVTLANLQDFKLDVQHVI EVDEGNTAVIACHLPESH PKAQVRYSVKQEWLEASRGNYLIM  
PSGNLQIVNASQEDEGMYKCAAYNPVTQEVKTS GSSDRLRVRRSTAEAAARI IYPPEAQTI  
IVTKGQSLILECVASGI PPRV TWAKDGSSVTGYNKTRFLLSNLLIDTTSEEDSGTYRCM  
ADNGVGQPGA AVILYNVQVFEPPEVTMELS QLVIPWGQSAKLTCEVRGNPPPSVLWL RNA  
VPLISSQRLRLSRRALRVLSMGPEDEGVYQCM AENEVGS AHAVVQLRTSRPSITPRLWQD  
AELATGTPPVSPSKLGNPEQMLRGQPALPRPPTS VGPASPKCPGKGGQAPAEAPIILSS  
PRTSKTDSYELVWRPRHEGSGRAPILYYVVKHRKQVTNSSDDWTISGIPANQHRLTLTRL  
DPGSLYEVEMAAAYNCAGEGQTAMVTFRTGRRPKPEIMASKEQQIQRDDPGAS PQSSSQPD  
HGRLSPPEAPDRPTISTASETSVYVTWIPRGNGGFPIQSFRVEYKKLKKVGDWILATSAI  
PPSRLSVEITGLEKGT SYKFRVRALNMLGESEPSAPSRPYVVS GYSGRVYERP VAGPYIT  
FTDAVNETTIMLKWMI IPASNNNTPIHGFIYYRPTDSNDSDYKKDMVEGDKYWHSISH  
LQPETSYDIKMOCFNEGGESEFSNVMICETKARKSSGQPGRLPPPTLAPPQPLPETIER  
PVG TGAMVARSSDLPYLI VGVVLG SIVLIIVTFIPFCLWRAWSKQKHTTDLGFP RSALPP  
SCPYTMVPLGGLPGHQASGQPYLSGISGRACANGIHMNRGCP SAAVGYPGMKPQQHCPGE  
LQQQSDTSSLLRQTHLGNGYDPQSHQITRGPKSSPDEGSFLYTL PDDSTHQLLQPHHDCC  
QRQEQPAAVGQSGVRRAPDSPVLEAVWDPPFHS GPPCCLGLVPVEEVDSPDSCQVSGGDW  
CPQHVPVGAYVGQEPGMQLSPGPLVRVVSFETPPLTI

**Signal peptide:**  
amino acids 1-30

**Transmembrane domain:**  
amino acids 16-30 (type II), 854-879



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**FIGURE 159**

CCCACGCGTCCGCCCCACGCGTCCGCCCCACGCGTCCGCCCCACGCGTCCGCCCCACGCGTCCG  
CCCACGCGTCCGCCCCACGCGTCCGGTGCAGCTCGCGCCGCACACTGCCTGGTGGAGGGA  
AGGAGCCCCGGGCGCCTCTCGCCGCTCCCCGCGCCCGCGTCCGCACCTCCCCACCGCCCCG  
CGCCCCGCGCCCGCCCCGCAAAGCATGAGTGAGCCCCGCTCTCTGCAGCTGCCCGGGG  
GCGAATGGCAGGCTGTTTCCGCGGAGTAAAGGTGGCGCCGGTCAGTGGTCTGTTTCCAAT  
GACGGACATTAACCAGACTGTCAGATCCTGGGGAGTCGCGAGCCCCGAGTTTGGAGTTTT  
TTCCCCCCCACAACGTACAGTCCGAAGTGCAGAGGGAAGGAAGGCGGCAGGAAGGCGAA  
GCTCGGGCTCCGGCACGTAGTTGGGAACTTGCGGGTCTAGAAAGTCGCCTCCCCGCCTT  
GCCGGCCGCCCTTGCAGCCCCGAGCCGAGCAGCAAAGTGAGACATTGTGCGCCTGCCAGA  
TCCGCCGGCCGCGGACCGGGGCTGCCTCGGAAACACAGAGGGGTCTTCTCTCGCCCTGCA  
TATAATTAGCCTGCACACAAAGGGAGCAGCTGAATGGAGGTTGTCACTCTCTGGAAAAGG  
ATTTCTGACCGAGCGCTTCCAATGGACATTCTCCAGTCTCTCTGGAAAGATTCTCGCTAA  
TGGATTTCCTGCTGCTCGGTCTCTGTCTATACTGGCTGCTGAGGAGGCCCTCGGGGTGG  
TCTTGTGTCTGCTGGGGGCTGCTTTCAGATGCTGCCCGCCGCCCCCAGCGGGTGCCCGC  
AGCTGTGCCGGTGCAGAGGGGCGGCTGCTGTACTGCGAGGCGCTCAACCTCACCGAGGCGC  
CCCACAACCTGTCCGGCCTGCTGGGCTTGTCCCTGCGCTACAACAGCCTCTCGGAGCTGC  
GCGCCGGCCAGTTACCGGGTTAATGCAGCTCACGTGGCTCTATCTGGATCACAATCACA  
TCTGCTCCGTGCAGGGGGACGCCTTTCAGAACTGCGCCGAGTTAAGGAACTCACGTGA  
GTTCCAACAGATCACCAACTGCCAACACCACCTTCCGGCCCATGCCAACCTGCGCA  
GCGTGGACCTCTCGTACAACAAGCTGCAGGCGCTCGCGCCCGACCTCTTCCACGGGCTGC  
GGAAGCTCACACGCTGCATATGCGGGCCAACGCCATCCAGTTTGTGCCCGTGCGCATCT  
TCCAGGACTGCCGCAGCCTCAAGTTTCTCGACATCGGATAACAATCAGCTCAAGAGTCTGG  
CGCGCAACTCTTTGCGCCGGCTTGTTTAAGCTCACCGAGCTGCACCTCGAGCACAACGACT  
TGGTCAAGGTGAACTTCGCCCCTTCCCGCGCCTCATCTCCCTGCACTCGCTCTGCCTGC  
GGAGGAACAAGGTGGCCATTGTGGTCAGCTCGCTGGAAGTGGGTTTGGAACTGGAGAAAA  
TGGACTTGTGCGGCAACGAGATCGAGTACATGGAGCCCCATGTGTTGAGACCGTGCCGC  
ACCTGCAGTCCCTGCAGCTGGACTCCAACCGCCTCACCTACATCGAGCCCCGGATCCTCA  
ACTCTTGGAAGTCCCTGACAAGCATCACCTGGCCGGGAACCTGTGGGATTGCGGGCGCA  
ACGTGTGTGCCCTAGCCTCGTGGCTCAGCAACTTCCAGGGGCGCTACGATGGCAACTTGC  
AGTGCGCCAGCCCGGAGTACGCACAGGGCGAGGACGTCTTGGACGCCGTGTACGCCTTCC  
ACCTGTGCGAGGATGGGGCCGAGCCACCAGCGGCCACCTGCTCTCGGCCGTACCAACC  
GCAGTGATCTGGGGCCCCCTGCCAGCTCGGCCACCACGCTCGCGGACGGCGGGGAGGGGC  
AGCACGACGGCACATTTCGAGCCTGCCACCGTGGCTCTTCCAGGCGGCGAGCACGCCGAGA  
ACGCCGTGCAGATCCACAAGGTGGTCACGGGCACCATGGCCCTCATCTTCTCCTTCTCA  
TCGTGGTCTTGGTGCTCTACGTGTCTGGAAGTGTTCAGCCAGCCTCAGGCAGCTCA  
GACAGTGCTTTGTACGCGAGCGCAGGAAGCAAAAGCAGAAACAGACCATGCATCAGATGG  
CTGCCATGTCTGCCAGGAATACTACGTTGATTACAAACCGAACCACATTGAGGGAGCCC  
TGGTGATCATCAACGAGTATGGCTCGTGTACCTGCCACCAGCAGCCCGCGAGGGAATGCG  
AGGTGTGATTGTCCCAGTGGCTCTCAACCCATGCGCTACCAAATACGCCTGGGCAGCCGG  
GACGGGCCGGCGGGCACCAGGCTGGGGTCTCCTTGTCTGTGCTCTGATATGCTCCTTGAC  
TGAAACTTTAAGGGGATCTCTCCAGAGACTTGACATTTTAGCTTTATTGTGTCTTAAAA  
ACAAAAGCGAATTAAACACAAACAAAAACCCACCCACAACTTCAGGACAGTCTATC  
TTAAATTTTATATGAGAACTCCTTCCCTCCCTTTGAAGATCTGTCCATATTGAGGAATCTG  
AGAGTGTAAGGAGGTGGCCATAAGACAGAGAGAGAATAATCGTGCTTTGTTTTATGCTA  
CTCCTCCACCCCTGCCCATGATTAAACATCATGTATGTAGAAGATCTTAAGTCCATACGC  
ATTTTCATGAAGAACCATTGGAAAGAGGAATCTGCAATCTGGGAGCTTAAGAGCAAATGAT

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GACCATAGAAAGCTATGTTCTTACTTTGTGTGTGTGTCTGTATGTTTCTGCGTTGTGTGT  
CTTTGTAGGCAAGCAAACGTTGTCTACACAAACGGGAATTTAGCTCACATCATTTCATGC  
CCCTGTGCCTCTAGCTCTGGAGATTGGTGGGGGGAGGTGGGGGGAAACGGCAGGAATAAG  
GGAAAGTGGTAGTTTTTAAGCTTCAAGAACTTGCTCTGACCCCTCTAAGCAAACCTACTAAGCATTTA  
ATTATCTTTAAGCTTCAAGAACTTGCTCTGACCCCTCTAAGCAAACCTACTAAGCATTTA  
AAAGAGAATCTAATTTTTTAAAGGTGTAGCACCTTTTTTTTTTATTCTTCCCACAGAGGGTG  
CTAATCTCATTATGCTGTGCTATCTGAAAAGAACTTAAGGCCACAATTCACGTCTCGTCC  
TGGGCATTGTGATGGATTGACCCCTCCATTTGCAGTACCTTCCCAGCTGATTAAAGTTCAG  
CAGTGGTATTGAGGTTTTTCGAATATTTATATAGAAAAAAGTCTTTTCACATGACAAAT  
GACACTCTCACACCAGTCTTAGCCCTAGTAGTTTTTTAGGTTGGACCAGAGGAAGCAGGT  
TAAATGAGACCTGTCCTCTGCTGCACTCAGAAAAAATAGGCAGTCCCTGATGCTCAGATC  
TTAGCCTTGATATTAATAGTTGAGACCACCTACCCACAATGCAGCCTATACTCCCAAGAC  
TACAAAGTTACCATCGCAAAGGAAAGGTTATTCCAGTAAAAGGAAATAGTTTTCTCAACC  
ATTTAAAAATATTCTTCTGAACTCATCAAAGTAGAAGAGCCCCAACCTTTTCTCTCTGC  
CTTCAAGAAGGCAGACATTTGGTATGATTTAGCATCAACAACACATTTATGAGTATATGT  
AAGTAATCAGAGGGGCAAATGCCACTTGTTATTCCTCCCAAGTTTTCCAAGCAAGTACAC  
ACAGATCTCTGGTAGGATTAGGGGCCACTTGTGTTTCCGGCTTATTTAGTCGACTTGTC  
AGCAAGTTTGATGCCTAGTCTATCTGACATGGCCCAGTAGAACAGGGCATTGATGGATCA  
CATGAGATGGTAGAAGGAACATCATCACATACCCCTCTCACAGAGAAAATTATCAAAGAA  
CCAGAAATTATATCTGTTTTGGAGCAAGAGTGTCTAATGTTTCAGGGTAGTCAAATAA  
ACATAAATTATCTCCTCTAGATGAGTGGCGATGTTGGCTGATTTGGGTCTGCCATTGACA  
GAATGTCAAATAAAAAGGAATTAGCTAGAATATGACCATTAAATGTGCTTCTGAAATATA  
TTTTGAGATAGGTTTAGAATGTCA

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**FIGURE 160**

MDFLLLGLCLYWLLRRRPSGVVLCLLGACFQMLPAAPSGCPQLCRCEGRLLYCEALNLTEA  
PHNLSGLLGLSLRYNSLSELRAGQFTGLMQLTWLYLDHNHICSVQGDAFQKLRRVKELTL  
SSNQITQLPNTTFRPMPNLRSDLSYNKLQALAPDLFHGLRKLTTLHMRANAIQFVPVRI  
FQDCRSCLKFLDIGYNQLKSLARNSFAGLFPKLTLEHNDLVKVNFAHFPRLLSLHSLCL  
RRNKVAIVVSSLDWVWNLEKMDLSGNEIEYMEPHVFETVPHLQSLQLDSNRLTYIEPRIL  
NSWKSLSITLAGNLWDCGRNVCALASWLSNFQGRYDGNLQCASPEYAQGEDVLDVAVAF  
HLCEDGAEPTSGHLLSAVTNRSDLGPPASSATTLADGGEGQHDGTFEPATVALPGGEHAE  
NAVQIHKVVTGTMALIFSFLIVVLVLYVSWKCFPASLRQLRQCFVTQRRKQKQKQTMHQM  
AAMSAQEYYVDYKPNHIEGALVIINEYGSTCHQQPARECEV



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**FIGURE 162**

MAPQSLPSSRMAPLGMLLGLLMAACFTFCLSHQNLKEFALTNPEKSSTKETERKETKAEE  
ELDAEVLEVFHPTHEWQALQPGQAVPAGSHVRLNLQTGEREAKLQYEDKFRNNLKGKRLD  
INTNTYTSQDLKSALAKFKEGAEMESSKEDKARQAEVKRLFRPIEELKKDFDELNVVIET  
DMQIMVRLINKFNSSSSSLEEKIAALFDLEYVHQMDNAQDLLSFGGLQVVINGLNSTEP  
LVKEYAAFVLGAAFSSNPKVQVEAIEGGALQKLLVILATEQPLTAKKKVLFALCSLLRHF  
PYAQRQFLKLGGGLQVLRTLQVEKGTEVLAVRVVTLTYDLVTEKMFEEEEAEELTQEMSPEK  
LQQYRQVHLLPGLWEQGWCEITAHLLALPEHDAREKVLQTLGVLLTTCRDRYRQDPQLGR  
TLASLQAEYQVLASLELQDGEDEGYFQELLGSVNSLLKELR

**Important features:**

**Signal peptide:**

amino acids 1-29

**Hypothetical YJL126w/YLR351c/yhcX family protein:**

amino acids 364-373

**N-glycosylation site:**

amino acids 193-197, 236-240

**N-myristoylation site:**

amino acids 15-21, 19-25, 234-240, 251-257, 402-408, 451-457

**Homologous region SLS1 protein:**

amino acids 68-340

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**FIGURE 163**

CAGAGAGGAGGCTTTGGGAATTGTCCAGCAGAAACAGAGAAGTCTGAGGTGGTGTCAAGA  
CAAAAGATGCTTCAGCTTTGGAACTTGTTCTCCTGTGCGGCGTGCTCACTGGGACCTCA  
GAGTCTCTTCTTGACAATCTTGGCAATGACCTAAGCAATGTCGTGGATAAGCTGGAACCT  
GTTCTTCACGAGGGACTTGAGACAGTTGACAATACTCTTAAAGGCATCCTTGAGAACTG  
AAGGTCGACCTAGGAGTGCTTCAGAAATCCAGTGCTTGGCAACTGGCCAAGCAGAAGGCC  
CAGGAAGCTGAGAAATTGCTGAACAATGTCATTTCTAAGCTGCTTCCAACTAACACGGAC  
ATTTTGGGTTGAAAATCAGCAACTCCCTCATCCTGGATGTCAAAGCTGAACCGATCGAT  
GATGGCAAAGGCCTTAACCTGAGCTTCCCTGTCACCGCGAATGTCACTGTGGCCGGGCCC  
ATCATTTGGCCAGATTATCAACCTGAAAGCCTCCTTGGACCTCCTGACCGCAGTCACAATT  
GAAACTGATCCCCAGACACACCAGCCTGTTGCCGTCTTGGGAGAATGCGCCAGTGACCCA  
ACCAGCATCTCACTTTCCTTGCTGGACAAACACAGCCAAATCATCAACAAGTTCGTGAAT  
AGCGTGATCAACACGCTGAAAAGCACTGTATCCTCCCTGCTGCAGAAGGAGATATGTCCA  
CTGATCCGCATCTTCATCCACTCCCTGGATGTGAATGTCATTTCAGCAGGTCGTCGATAAT  
CCTCAGCACAAAACCCAGCTGCAAACCCTCATCTGAAGAGGACGAATGAGGAGGACCACT  
GTGGTGCATGCTGATTGGTTCCAGTGGCTTGCCCCACCCCCTTATAGCATCTCCCTCCA  
GGAAGCTGCTGCCACCACCTAACCAGCGTGAAAGCCTGAGTCCCACCAGAAGGACCTTCC  
CAGATACCCCTTCTCCTCACAGTCAGAACAGCAGCCTCTACACATGTTGTCTGCCCCCTG  
GCAATAAAGGCCCATTTCTGCACCCTTAA

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**FIGURE 164**

MLQLWKLVLGCVLTGTSESLLDNLGNDLSNVVDKLEPVLHEGLETVDNTLKGILEKLKV  
DLGVLOKSSAWQLAKQKAQEAELNNVISKLLPTNTDIFGLKISNSLIIDVKAEPIDDG  
KGLNLSFPVTANVTVAGPIIGQIINLKASLDLLTAVTIETDPQTHQPVAVLGECDPTS  
ISLSLLDKHSQIINKFVNSVINTLKSTVSSLLQKEICPLIRIFIHSLDVNVIQQVVDNPQ  
HKTQLQTLI

**Important features:****Signal peptide:**

1-15

**Transmembrane domain:**

none

**N-glycosylation site:**

124-128, 132-136

**N-myristoylation site:**

12-18, 16-22, 26-32, 101-107, 122-128, 141-147

**Leucine zipper pattern:**

44-66

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**FIGURE 165**

GCAGTCAGAGACTTCCCCTGCCCTCGCTGGGAAAGAACATTAGGAATGCCTTTTAGTGCC  
CTTGCTTCCTGAACTAGCTCACAGTAGCCCGGCGGCCAGGGCAATCCGACCACATTTCA  
CTCTCACCGCTGTAGGAATCCAGATGCAGGCCAAGTACAGCAGCACGAGGGACATGCTGG  
ATGATGATGGGGACACCACCATGAGCCTGCATTCTCAAGCCTCTGCCACAACCTCGGCATC  
CAGAGCCCCGGCGCACAGAGCAGAGGGCTCCCTCTTCAACGTGGCGACCAGTGGCCCTGA  
CCCTGCTGACTTTGTGCTTGGTGCTGCTGATAGGGCTGGCAGCCCTGGGGCTTTTGT  
TTCAGTACTACCAGCTCTCCAATACTGGTCAAGACACCATTTCTCAAATGGAAGAAAGAT  
TAGGAAATACGTCCCAAGAGTTGCAATCTCTTCAAGTCCAGAATATAAAGCTTGCAGGAA  
GTCTGCAGCATGTGGCTGAAAACTCTGTCTGTGAGCTGTATAACAAAGCTGGAGCACACA  
GGTGCAGCCCTTGTACAGAACAATGGAAATGGCATGGAGACAATTGCTACCAGTTCTATA  
AAGACAGCAAAAGTTGGGAGGACTGTAAATATTTCTGCCTTAGTGAAAACTCTACCATGC  
TGAAGATAAACAAACAAGAAGACCTGGAATTTGCCGCGTCTCAGAGCTACTCTGAGTTTT  
TCTACTCTTATTGGACAGGGCTTTTGCGCCCTGACAGTGGCAAGGCCTGGCTGTGGATGG  
ATGGAACCCCTTTCACCTCTGAACTGTTCCATATTATAATAGATGTCACCAGCCCCAAGAA  
GCAGAGACTGTGTGGCCATCCTCAATGGGATGATCTTCTCAAAGGACTGCAAAGAATTGA  
AGCGTTGTGTCTGTGAGAGAAGGGCAGGAATGGTGAAGCCAGAGAGCCTCCATGTCCCCC  
CTGAAACATTAGGCGAAGGTGACTGATTCGCCCTCTGCAACTACAAATAGCAGAGTGAGC  
CAGGCGGTGCCAAAGCAAGGGCTAGTTGAGACATTGGGAAATGGAACATAATCAGGAAAG  
ACTATCTCTCTGACTAGTACAAAATGGGTTCTCGTGTTTCTGTTCAGGATCACCAGCAT  
TTCTGAGCTTGGGTTTATGCACGTATTTAACAGTCACAAGAAGTCTTATTTACATGCCAC  
CAACCAACCTCAGAAACCCATAATGTCATCTGCCTTCTTGGCTTAGAGATAACTTTTAGC  
TCTCTTCTCTCAATGTCTAATATCACCTCCCTGTTTTTCATGTCTTCCTTACACTTGGT  
GGAATAAGAACTTTTTGAAGTAGAGGAAATACATTGAGGTAACATCCTTTTCTCTGACA  
GTCAAGTAGTCCATCAGAAATTGGCAGTCACTTCCCAGATTGTACCAGCAAATACACAAG  
GAATTCCTTTTGTGTTTTCAGTTCATACTAGTCCCTTCCCAATCCATCAGTAAAGACCC  
CATCTGCCTTGTCCATGCCGTTTCCCAACAGGGATGTCACTTGATATGAGAATCTCAAT  
CTCAATGCCTTATAAGCATTCTTCCCTGTGTCCATTAAGACTCTGATAATTGTCTCCCT  
CCATAGGAATTTCTCCCAGGAAAGAAATATATCCCCATCTCCGTTTCATATCAGAACTAC  
CGTCCCCGATATTCCTTCAGAGAGATTAAAGACCAGAAAAAAGTGAGCCTCTTCATCTG  
CACCTGTAATAGTTTCAGTTCCTATTTTCTTCCATTGACCCATATTTATACCTTTCAGGT  
ACTGAAGATTTAATAATAATAAATGTAAATACTGTGAAAAA



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**FIGURE 166**

MQAKYSSTRDMLDDDGDTTMSLHSQASATTRHPEPRRTEHRAPSSTWRPVALTLLTLCV  
LLIGLAALGLLFFQYYQLSNTGQDTISQMEERLGNTSQELQSLQVQNIKLAGSLQHVAEK  
LCRELYNKAGAHRCSPCTEQWKWHGDNCYQFYKDSKSWEDCKYFCLSENSTMLKINKQED  
LEFAASQSYSEFFYSYWTGLLRPD SGKAWLWMDGTPFTSELFHIIIDVTSPRSRDCVAIL  
NGMIFSKDCKELKRCVCERRAGMVKPESLHVPPETLGEGD

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**FIGURE 167**

GCGACGGGCAGGACGCCCCGTTGCGCTAGCGCGTGCTCAGGAGTTGGTGTCTGCTGCG  
CTCAGGATGAGGGGGAATCTGGCCCTGGTGGGCGTTCTAATCAGCCTGGCCTTCCTGTCA  
CTGCTGCCATCTGGACATCCTCAGCCGGCTGGCGATGACGCCTGCTCTGTGCAGATCCTC  
GTCCCTGGCCTCAAAGGGGATGCGGGAGAGAAGGGAGACAAAGGCGCCCCGGACGGCCT  
GGAAGAGTCGGCCCCACGGGAGAAAAAGGAGACATGGGGGACAAAGGACAGAAAGGCAGT  
GTGGGTCGTTCATGGAAAAATTGGTCCCATTGGGCTCTAAAGGTGAGAAAGGAGATTCCGGT  
GACATAGGACCCCCCTGGTCCTAATGGAGAACCAGGCCTCCCATGTGAGTGCAGCCAGCTG  
CGCAAGGCCATCGGGGAGATGGACAACCAGGTCTCTCAGCTGACCAGCGAGCTCAAGTTC  
ATCAAGAATGCTGTGCGCCGGTGTGCGCGAGACGGAGAGCAAGATCTACCTGCTGGTGAAG  
GAGGAGAAGCGCTACGCGGACGCCCAGCTGTCTGCCAGGGCCGCGGGGGCACGCTGAGC  
ATGCCCAAGGACGAGGCTGCCAATGGCCTGATGGCCGCATACCTGGCGCAAGCCGGCCTG  
GCCCCGTGTCTTCATCGGCATCAACGACCTGGAGAAGGAGGGCGCCTTCGTGTACTCTGAC  
CACTCCCCCATGCGGACCTTCAACAAGTGGCGCAGCGGTGAGCCCAACAATGCCTACGAC  
GAGGAGGACTGCGTGGAGATGGTGGCCTCGGGCGGCTGGAACGACGTGGCCTGCCACACC  
ACCATGTACTTCATGTGTGAGTTTGACAAGGAGAACATGTGAGCCCTCAGGCTGGGGCTGC  
CCATTGGGGGCCCCACATGTCCCTGCAGGGTTGGCAGGGACAGAGCCCAGACCATGGTGC  
CAGCCAGGGAGCTGTCCCTCTGTGAAGGTGGAGGCTCACTGAGTAGAGGGCTGTTGTCT  
AAACTGAGAAAATGGCCTATGCTTAAGAGGAAAATGAAAGTGTTCTGGGGTGCTGTCTC  
TGAAGAAGCAGAGTTTCATTACCTGTATTGTAGCCCCAATGTCATTATGTAATTATTACC  
CAGAATTGCTCTTCCATAAAGCTTGTGCCTTTGTCCAAGCTATACAATAAAATCTTTAAG  
TAGTGCAGTAGTTAAGTCCAAAAAAAAAAAAAAAAAAAAA

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## FIGURE 168

MRGNLALVGVLI SLAFLSLLPSGHPQPAGDDACSVQILVPGLKGDAGEKGDKGAPGRPGR  
VGPTGEKGDMDKGQKGSVGRHGKIGPIGSKGEKGDSDIGPPGPNGEPGLPCECSQLRK  
AIGEMDNQVSQLTSELKFIKNAVAGVRETESKIYLLVKEEKRYADAQLSCQGRGGLSMP  
KDEAANGLMAAYLAQAGLARVFIGINDLEKEGAFVYSDHSPMRTFNKWRSGEPNNAYDEE  
DCVEMVASGGWNDVACHTTMYFMCEFDKENM

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**FIGURE 169**

AGTGACTGCAGCCTTCCTAGATCCCCTCCACTCGGTTTCTCTCTTTGCAGGAGCACCGGC  
AGCACCAGTGTGTGAGGGGAGCAGGCAGCGGTCCTAGCCAGTTCCTTGATCCTGCCAGAC  
CAGCCAGCCCCCGGCACAGAGCTGCTCCACAGGCACCAATGAGGATCATGCTGCTATTAC  
AGCCATCCTGGCCTTCAGCCTAGCTCAGAGCTTTGGGGCTGTCTGTAAGGAGCCACAGGA  
GGAGGTGGTTCCTGGCGGGGGCCGCAGCAAGAGGGATCCAGATCTCTACCAGCTGCTCCA  
GAGACTCTTCAAAAGCCACTCATCTCTGGAGGGATTGCTCAAAGCCCTGAGCCAGGCTAG  
CACAGATCCTAAGGAATCAACATCTCCCGAGAAACGTGACATGCATGACTTCTTTGTGGG  
ACTTATGGGCAAGAGGAGCGTCCAGCCAGAGGGAAAGACAGGACCTTTCTTACCTTCAGT  
GAGGGTTCCTCGGCCCTTCATCCCAATCAGCTTGGATCCACAGGAAAGTCTTCCCTGGG  
AACAGAGGAGCAGAGACCTTTATAAGACTCTCCTACGGATGTGAATCAAGAGAACGTCCC  
CAGCTTTGGCATCCTCAAGTATCCCCGAGAGCAGAATAGGTACTCCACTTCCGGACTCC  
TGGACTGCATTAGGAAGACCTCTTCCCTGTCCCAATCCCAGGTGCGCACGCTCCTGTT  
ACCCTTTCTCTTCCCTGTTCTTGTAACATTCTTGCTTTGACTCCTTCTCCATCTTTTC  
TACCTGACCCTGGTGTGGAACTGCATAGTGAATATCCCCAACCCCAATGGGCATTGACT  
GTAGAATACCCTAGAGTTCCTGTAGTGTCTACATTAAAAATATAATGTCTCTCTATT  
CCTCAACAATAAAGGATTTTTGCATATGAAAAAAAAAAAAAAAAAAAAAAAAAAAAA  
AAAAAAAAAAAA

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## FIGURE 170

MRIMLLFTAILAFSLAQSFQAVCKEPQEEVVPGGGRSKRDPDLYQLLQRLFKSHSSLEGL  
LKALSQASTDPKESTSPKRDMDHDFVGLMGKRSVQPEGKTGPFLPSVRVPRPLHPNQLG  
STGKSSLGTEEQRPL

**Important features:**

**Signal peptide:**

amino acids 1-18

**Tyrosine kinase phosphorylation site:**

amino acids 36-45

**N-myristoylation site:**

amino acids 33-39, 59-65

**Amidation site:**

amino acids 90-94

**Leucine zipper pattern:**

amino acids 43-65

**Tachykinin family signature:**

amino acids 86-92

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**FIGURE 171**

TGGCCTCCCCAGCTTGCCAGGCACAAGGCTGAGCGGGAGGAAGCGAGAGGCATCTAAGCA  
GGCAGTGTTTTGCCTTCACCCCAAGTGACCATGAGAGGTGCCACGCGAGTCTCAATCATG  
CTCCTCCTAGTAACTGTGTCTGACTGTGCTGTGATCACAGGGGCCTGTGAGCGGGATGTC  
CAGTGTGGGGCAGGCACCTGCTGTGCCATCAGCCTGTGGCTTCGAGGGCTGCGGATGTGC  
ACCCCGCTGGGGCGGGAAGGCGAGGAGTGCCACCCCGGCAGCCACAAGGTCCCCTTCTTC  
AGGAAACGCAAGCACACACCTGTCCTTGCTTGCCCAACCTGCTGTGCTCCAGGTTCCCG  
GACGGCAGGTACCGCTGCTCCATGGACTTGAAGAACATCAATTTTTAGGCGCTTGCCCTGG  
TCTCAGGATACCCACCATCCTTTTCTGAGCACAGCCTGGATTTTTATTTCTGCCATGAA  
ACCCAGCTCCCATGACTCTCCAGTCCCTACACTGACTACCCTGATCTCTCTTGTCTAGT  
ACGCACATATGCACACAGGCAGACATACCTCCCATCATGACATGGTCCCAGGCTGGCCT  
GAGGATGTACAGCTTGAGGCTGTGGTGTGAAAGGTGGCCAGCCTGGTTCTCTTCCCTGC  
TCAGGCTGCCAGAGAGGTGGTAAATGGCAGAAAGGACATTCCCCCTCCCCTCCCAGGTG  
ACCTGCTCTCTTTCCTGGGCCCTGCCCCCTCTCCCCACATGTATCCCTCGGTCTGAATTAG  
ACATTCTTGGGCACAGGCTCTTGGGTGCATTGCTCAGAGTCCCAGGTCTTGGCCTGACCC  
TCAGGCCCTTCACGTGAGGTCTGTGAGGACCAATTTGTGGGTAGTTCATCTTCCCTCGAT  
TGGTTAACTCCTTAGTTTCAGACCACAGACTCAAGATTGGCTCTTCCCAGAGGGCAGCAG  
ACAGTCACCCCAAGGCAGGTGTAGGGAGCCCAGGGAGGCCAATCAGCCCCCTGAAGACTC  
TGGTCCCAGTCAGCCTGTGGCTTGTGGCCTGTGACCTGTGACCTTCTGCCAGAATTGTCA  
TGCCTCTGAGGCCCCCTCTTACCACACTTTACCAGTTAACCCTGAAGCCCCCAATTCCC  
ACAGCTTTTCCATTAAAATGCAATGGTGGTGGTTCAATCTAATCTGATATTGACATATT  
AGAAGGCAATTAGGGTGTTCCTTAAACAACTCCTTTCCAAGGATCAGCCCTGAGAGCAG  
GTTGGTGACTTTGAGGAGGGCAGTCCTCTGTCCAGATTGGGGTGGGAGCAAGGGACAGGG  
AGCAGGGCAGGGGCTGAAAGGGGCACTGATTTCAGACCAGGGAGGCAACTACACACCAACA  
TGCTGGCTTTAGAATAAAAGCACCAACTGAAAAA

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## FIGURE 172

MRGATRVSIMLLLVTVSDCAVITGACERDVQCGAGTCCAI SLWLRGLRMCTPLGREGEEC  
HPGSHKVPFFRKRKHHTCPCLPNLLCSRFPDGRYRCSMDLKNINF

**Signal peptide:**  
amino acids 1-19

**Tyrosine kinase phosphorylation site:**  
amino acids 88-95

**N-myristoylation sites:**  
amino acids 33-39, 35-41, 46-52

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**FIGURE 173**

AGCGCCCGGGCGTCGGGGCGGTAAAAGGCCGGCAGAAAGGGAGGCACCTTGAGAAATGTCCTT  
TCCTCCAGGACCCAAGTTTCTTCACCATGGGGATGTGGTCCATTGGTGCAGGAGCCCTGG  
GGGCTGCTGCCTTGGCATTGCTGCTTGCCAAACACAGACGTGTTTCTGTCCAAGCCCCAGA  
AAGCGGCCCTGGAGTACCTGGAGGATATAGACCTGAAAACACTGGAGAAGGAACCAAGGA  
CTTTCAAAGCAAAGGAGCTATGGGAAAAAATGGAGCTGTGATTATGGCCGTGCGGAGGC  
CAGGCTGTTTCCTCTGTGCGAGAGGAAGCTGCGGATCTGTCCTCCCTGAAAAGCATGTTGG  
ACCAGCTGGGCGTCCCCCTCTATGCAGTGGTAAAGGAGCACATCAGGACTGAAGTGAAGG  
ATTTCCAGCCTTATTTCAAAGGAGAAATCTTCCTGGATGAAAAGAAAAAGTTCATGGTC  
CACAAAGGCGGAAGATGATGTTTATGGGATTTATCCGTCTGGGAGTGTGGTACAACCTTCT  
TCCGAGCCTGGAACGGAGGCTTCTCTGGAAACCTGGAAGGAGAAGGCTTCATCCTTGGGG  
GAGTTTTTCGTGGTGGGATCAGGAAAGCAGGGCATTCTTCTTGAGCACCAGAAAAAGAAT  
TTGGAGACAAAGTAAACCTACTTTCTGTTCTGGAAGCTGCTAAGATGATCAAACCACAGA  
CTTTGGCCTCAGAGAAAAAATGATTGTGTGAAACTGCCAGCTCAGGGATAACCAGGGAC  
ATTCACCTGTGTTTATGGGATGTATTGTTTCCACTCGTGTCCCTAAGGAGTGAGAAACCC  
ATTTATACTCTACTCTCAGTATGGATTATTAATGTATTTAATATTCTGTTTAGGCCAC  
TAAGGCAAAATAGCCCCAAAACAAGACTGACAAAAATCTGAAAACTAATGAGGATTATT  
AAGCTAAAACCTGGGAAATAGGAGGCTTAAAATTGACTGCCAGGCTGGGTGCAGTGGCTC  
ACACCTGTAATCCCAGCACTTTGGGAGGCCAAGGTGAGCAAGTCACTTGAGGTCGGGAGT  
TCGAGACCAGCCTGAGCAACATGGCGAAACCCCGTCTCTACTAAAAATACAAAAATCACC  
CGGGTGTGGTGGCAGGCACCTGTAGTCCCAGCTACCCGGGAGGCTGAGGCAGGAGAATCA  
CTTGAACCTGGGAGGTGGAGGTTGCGGTGAGCTGAGATCACACCACTGTATTCCAGCCTG  
GGTGA CTGAGACTCTAACTAA



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**FIGURE 174**

MSFLQDPSFFTGMWWSIGAGALGAAALALLANTDVFLSKPQKALEYLEDIDLKTLEKE  
PRTFKAKELWEKNGAVIMAVRRPGCFLCREEAADLSSLKSMLDQLGVPLYAVVKEHIRTE  
VKDFQPYFKGEIFLDEKKKFYGPQRRKMMFMGFIRLGWYNFFRAWNGGFSGNLEGEFGFI  
LGGVFVVGSGKQGILLEHREKEFGDKVNLLSVLEAAKMIKPQTLASEKK

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**FIGURE 175**

GACAGTGGAGGGCAGTGGAGAGGACCGCGCTGTCCTGCTGTACCAAGAGCTGGAGACAC  
CATCTCCCACCGAGAGTCATGGCCCCATTGGCCCTGCACCTCCTCGTCTCGTCCCCATC  
CTCCTCAGCCTGGTGGCCTCCCAGGACTGGAAGGCTGAACGCAGCCAAGACCCCTTCGAG  
AAATGCATGCAGGATCCTGACTATGAGCAGCTGCTCAAGGTGGTGACCTGGGGGCTCAAT  
CGGACCCTGAAGCCCCAGAGGGTGATTGTGGTTGGCGCTGGTGTGGCCGGGCTGGTGGCC  
GCCAAGGTGCTCAGCGATGCTGGACACAAGGTCAACATCCTGGAGGCAGATAACAGGATC  
GGGGGCCGCATCTTACCTACCGGGACCAGAACACGGGCTGGATTGGGGAGCTGGGAGCC  
ATGCGCATGCCCAGCTCTCACAGGATCCTCCACAAGCTCTGCCAGGGCCTGGGGCTCAAC  
CTGACCAAGTTCACCCAGTACGACAAGAACACGTGGACGGAGGTGCACGAAGTGAAGCTG  
CGCAACTATGTGGTGGAGAAGGTGCCCGAGAAGCTGGGCTACGCCTTGCGTCCCCAGGAA  
AAGGGCCACTCGCCCCGAAGACATCTACCAGATGGCTCTCAACCAGGCCCTCAAAGACCTC  
AAGGCACTGGGCTGCAGAAAGGCGATGAAGAAGTTTGAAAGGCACACGCTCTTGGAATAT  
CTTCTCGGGGAGGGGAACCTGAGCCGGCCGGCCGTGCAGCTTCTGGGAGACGTGATGTCC  
GAGGATGGCTTCTTCTATCTCAGCTTCGCCGAGGCCCTCCGGGCCCCACAGCTGCCTCAGC  
GACAGACTCCAGTACAGCCGCATCGTGGGTGGCTGGGACCTGCTGCCGCGCGCGCTGCTG  
AGCTCGCTGTCCGGGCTTGTGCTGTTGAACGCGCCCGTGTTGGCGATGACCCAGGGACCG  
CACGATGTGCACGTGCAGATCGAGACCTCTCCCCGGCGCGGAATCTGAAGGTGCTGAAG  
GCCGACGTGGTGCTGCTGACGGCGAGCGGACCGGCGGTGAAGCGCATCACCTTCTCGCCG  
CCGCTGCCCCGCCACATGCAGGAGGCGCTGCGGAGGCTGCACTACGTGCCGGCCACCAAG  
GTGTTCCCTAAGCTTCCGCAGGCCCTTCTGGCGCGAGGAGCACATTGAAGGCGGCCACTCA  
AACACCGATCGCCCGTCGCGCATGATTTTCTACCCGCCGCGCGCGAGGGCGCGCTGCTG  
CTGGCCTCGTACACGTGGTCGGACGCGGCGGCAGCGTTCGCCGGCTTGAGCCGGGAAGAG  
GCGTTGCGCTTGGCGCTCGACGACGTGGCGGCATTGCACGGGCCTGTCGTGCGCCAGCTC  
TGGGACGGCACCGGCGTCTCAAGCGTTGGGCGGAGGACCAGCACAGCCAGGGTGGCTTT  
GTGGTACAGCCCGCGGCTCTGGCAAACCGAAAAGGATGACTGGACGGTCCCTTATGGC  
CGCATCTACTTTGCCGGCGAGCACACCGCCTACCCGCACGGCTGGGTGGAGACGGCGGTTC  
AAGTCGGCGCTGCGCGCCGCCATCAAGATCAACAGCCGGAAGGGGCCTGCATCGGACACG  
GCCAGCCCCGAGGGGCACGCATCTGACATGGAGGGGCAGGGGCATGTGCATGGGGTGGCC  
AGCAGCCCCCTCGCATGACCTGGCAAAGGAAGAAGGCAGCCACCCTCCAGTCCAAGGCCAG  
TTATCTCTCCAAAACACGACCCACACGAGGACCTCGCATTAAAGTATTTTCGGAAAAAAA  
AA

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**FIGURE 176**

MAPLALHLLVLVPILLSLVASQDWKAERSQDPFEKCMQDPDYEQLLKVVVTWGLNRTLKPQ  
RVIVVGAGVAGLVAAKVLSDAGHKVTILEADNRIGGRIFTYRDQNTGWIGELGAMRMPSS  
HRILHKLCQGLGLNLTKFTQYDKNTWTEVHEVKLRNYVVEKVPEKLGALRPQEKGHSPE  
DIYQMALNQALKDLKALGCRKAMKKFERHTLLEYLLGEGNLSRPAVQLLGDVMSSEDGFFY  
LSFAEALRAHSCLSDRLQYSRIVGGWDLPRALLSSLSGLVLLNAPVVAMTQGPHDVHVQ  
IETSPARNLKVLKADVLLTASGPAVKRITFSPPLPRHMQEALRRLHYVPATKVFLSFR  
RPFWREEHIEGGSNTDRPSRMIFYPPREGALLASYTWSDAAAAFAGLSREEALRLAL  
DDVAALHGPVVRQLWDGTGVVKRWAEDQHSQGGFVVQPPALWQTEKDDWTVPYGRIYFAG  
EHTAYPHGWVETAVKSALRAAIKINSRKGPASDTASPEGHASDMEGQGHVHGVASSPSHD  
LAKEEGSHPPVQGQLSLQNTTHTRTSH

**Signal peptide:**  
amino acids 1-21

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**FIGURE 177**

CCGGGGAGGGGAGGGCCCGTCCCGCCCCCTCCCCGTCTCTCCCCGCCCCCTCCCCGTCCCTC  
CCGCCGAAGCTCCGTCCCGCCCCGCGGGCCGGCTCCGCCCTCACCTCCCGGCCGCGGCTGC  
CCTCTGCCCCGGGTTGTCCAAGATGGAGGGCGCTCCACCGGGGTCGCTCGCCCTCCGGCTC  
CTGCTGTTTCGTGGCGCTACCCGCCTCCGGCTGGCTGACGACGGGCGCCCCGAGCCGCCG  
CCGCTGTCCGGAGCCCCACAGGACGGCATCAGAATTAATGTAACCTACACTGAAAGATGAT  
GGGGACATATCTAAACAGCAGGTTGTTCTTAACATAACCTATGAGAGTGGACAGGTGTAT  
GTAAATGACTTACCTGTAAATAGTGGTGTAAACCCGAATAAGCTGTCAGACTTTGATAGTG  
AAGAATGAAAATCTTGAAAATTTGGAGGAAAAAGAATATTTTGGAATTGTCAGTGTAAGG  
ATTTTAGTTTCATGAGTGGCCTATGACATCTGGTTCCAGTTTGCAACTAATTGTCATTCAA  
GAAGAGGTAGTAGAGATTGATGGAAAACAAGTTCAGCAAAAGGATGTCAGTGAATTGAT  
ATTTTAGTTAAGAACCGGGGAGTACTCAGACATTCAAACCTATACCCTCCCTTTGGAAGAA  
AGCATGCTCTACTCTATTTCTCGAGACAGTGACATTTTATTTACCCTTCCTAACCTCTCC  
AAAAAAGAAAGTGTTAGTTCACTGCAAACCACTAGCCAGTATCTTATCAGGAATGTGGAA  
ACCACTGTAGATGAAGATGTTTTACCTGGCAAGTTACCTGAAACTCCTCTCAGAGCAGAG  
CCGCCATCTTCATATAAGGTAATGTGTGTCAGTGGATGGAAAAGTTTAGAAAAGATCTGTGT  
AGGTTCTGGAGCAACGTTTTCCCAAGTATTCTTTTCAGTTTTTTGAACATCATGGTGGTTGGA  
ATTACAGGAGCAGCTGTGGTAATAACCATCTTAAAGGTGTTTTTCCCAGTTTCTGAATAC  
AAAGGAATTCTTCAGTTGGATAAAAGTGGACGTCATACCTGTGACAGCTATCAACTTATAT  
CCAGATGGTCCAGAGAAAAGAGCTGAAAACCTTGAAGATAAAACATGTATTTAAAACGCC  
ATCTCATATCATGGACTCCGAAGTAGCCTGTTGCCTCCAAATTTGCCACTTGAATATAAT  
TTTCTTTAAATCGTT

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**FIGURE 178**

MEGAPPGSLALRLLLLFVALPASGWLTGTAPEPPPLSGAPQDGIRINVTTLKDDGDISKQQ  
VVLNITYESGQVYVNDLPVNSGVTRISCQTLIVKNENLENLEEKEYFGIVSVRILVHEWP  
MTSGSSLQLIVIQEEVVEIDGKQVQOKDVTEIDILVKNRGVLRHSNYTLPLEESMLYSIS  
RDS DILFTLPNLSKKESVSSLQTTSQYLIRNVETTVDVLPGLPETPLRAEPPSSYKV  
MCQWMEKFRKDLCRFWSNVFPVFFQFLNIMVVGITGAADVITILKVFFPVSEYKGILQLD  
KVDVIPVTAINLYPDGPEKRAENLEDKTCI

**Signal peptide:**

1-23

**Transmembrane domain:**

266-284

**Leucine zipper pattern:**

155-177

**N-glycosylation site:**

46-50, 64-68, 166-170, 191-195

**Motif name: N-myristoylation site:**

3-9, 42-48, 273-279

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**FIGURE 179**

CTCCTTAGGTGGAAACCCTGGGAGTAGAGTACTGACAGCAAAGACCGGGAAAGACCATAC  
GTCCCCGGGCAGGGGTGACAACAGGTGTCATCTTTTTGATCTCGTGTGTGGCTGCCTTCC  
TATTTCAAGGAAAGACGCCAAGGTAATTTTGACCCAGAGGAGCAATGATGTAGCCACCTC  
CTAACCTTCCCTTCTTGAACCCCCAGTTATGCCAGGATTTACTAGAGAGTGTCAACTCAA  
CCAGCAAGCGGCTCCTTCGGCTTAACCTTGTGGTTGGAGGAGAGAACCCTTGTGGGGCTGC  
GTTCTCTTAGCAGTGCTCAGAAGTGACTTGCCTGAGGGTGGACCAGAAGAAAGGAAAGGT  
CCCCCTCTTGCTGTTGGCTGCACATCAGGAAGGCTGTGATGGGAATGAAGGTGAAAACCTTG  
GAGATTTCACTTCAGTCATTGCTTCTGCCTGCAAGATCATCCTTTAAAAGTAGAGAAGCT  
GCTCTGTGTGGTGGTTAACTCCAAGAGGCAGAACTCGTTCTAGAAGGAAATGGATGCAAG  
CAGCTCCGGGGGGCCCCAAACGCATGCTTCTGTGGTCTAGCCCAGGGAAGCCCTTCCGTG  
GGGGCCCCGGCTTTGAGGGATGCCACCGGTTCTGGACGCATGGCTGATTCTGAATGATG  
ATGGTTTCGCCGGGGGCTGCTTGCCTGGATTTCCTGGGTGGTGGTTTGTCTGGTGCTCCTC  
TGCTGTGCTATCTCTGTCTGTACATGTTGGCCTGCACCCCAAAGGTGACGAGGAGCAG  
CTGGCACTGCCCAGGGCCAACAGCCCCACGGGGAAGGAGGGGTACCAGGCCGTCTTCAG  
GAGTGGGAGGAGCAGCACCGCAACTACGTGAGCAGCCTGAAGCGGCAGATCGCACAGCTC  
AAGGAGGAGCTGCAGGAGAGGAGTGAGCAGCTCAGGAATGGGCAGTACCAAGCCAGCGAT  
GCTGCTGGCCTGGGTCTGGACAGGAGCCCCCAGAGAAAACCAGGCCGACCTCCTGGCC  
TTCCTGCACTCGCAGGTGGACAAGGCAGAGGTGAATGCTGGCGTCAAGCTGGCCACAGAG  
TATGCAGCAGTGCCTTTCGATAGCTTTACTCTACAGAAGGTGTACCAGCTGGAGACTGGC  
CTTACCCGCCACCCCGAGGAGAAGCCTGTGAGGAAGGACAAGCGGGATGAGTTGGTGGAA  
GCCATTGAATCAGCCTTGGAGACCCTGAACAATCCTGCAGAGAACAGCCCCAATCACCGT  
CCTTACACGGCCTCTGATTTCATAGAAGGGATCTACCGAACAGAAAGGGACAAAGGGACA  
TTGTATGAGCTCACCTTCAAAGGGGACCACAAACACGAATTCAAACGGCTCATCTTATTT  
CGACCATTTCAGCCCCATCATGAAAGTGAAAAATGAAAAGCTCAACATGGCCAACACGCTT  
ATCAATGTTATCGTGCCTCTAGCAAAAAGGGTGGACAAGTTCGGGCAGTTTCATGCAGAA  
TTCAGGGAGATGTGCATTGAGCAGGATGGGAGAGTCCATCTCACTGTTGTTTACTTTGGG  
AAAGAAGAAATAAATGAAGTCAAAGGAATACTTGAAAACACTTCCAAAGCTGCCAACTTC  
AGGAACTTTACCTTCATCCAGCTGAATGGAGAATTTTCTCGGGGAAAGGGACTTGATGTT  
GGAGCCCCGCTTCTGGAAGGGAAGCAACGTCTCTCTTTTCTGTGATGTGGACATCTAC  
TTCACATCTGAATTCCTCAATACGTGTAGGCTGAATACACAGCCAGGGAAGAAGGTATTT  
TATCCAGTTCTTTTCAGTCAGTACAATCCTGGCATAATATACGGCCACCATGATGCAGTC  
CCTCCCTTGGAAACAGCAGCTGGTCATAAAGAAGGAACTGGATTTTGGAGAGACTTTGGA  
TTTGGGATGACGTGTGAGTATCGGTGAGACTTCATCAATATAGGTGGGTTTGATCTGGAC  
ATCAAAGGCTGGGGCGGAGAGGATGTGCACCTTTATCGCAAGTATCTCCACAGCAACCTC  
ATAGTGGTACGGACGCCTGTGCGAGGACTCTTCCACCTCTGGCATGAGAAGCGCTGCATG  
GACGAGCTGACCCCCGAGCAGTACAAGATGTGCATGCAGTCCAAGGCCATGAACGAGGCA  
TCCCACGGCCAGCTGGGCATGCTGGTGTTCAGGCACGAGATAGAGGCTCACCTTCGCAAA  
CAGAAACAGAAGACAAGTAGCAAAAAACATGAACCTCCAGAGAAGGATTGTGGGAGACA  
CTTTTTCTTTCTTTTTCGAATTACTGAAAGTGGCTGCAACAGAGAAAAGACTTCCATAAA  
GGACGACAAAAGAAATTGGACTGATGGGTGAGAGATGAGAAAAGCCTCCGATTTCTCTCTGT  
TGGGCTTTTTTACAACAGAAATCAAAATCTCCGCTTTGCCTGCAAAAGTAACCCAGTTGCA  
CCCTGTGAAGTGTCTGACAAAGGCAGAATGCTTGTGAGATTATAAGCCTAATGGTGTGGA  
GGTTTTGATGGTGTTTACAATACACTGAGACCTGTTGTTTTGTGTGCTCATTGAAATATT  
CATGATTTAAGAGCAGTTTTGTAAAAAATTCATTAGCATGAAAGGCAAGCATATTTCTCC  
TCATATGAATGAGCCTATCAGCAGGGCTCTAGTTTCTAGGAATGCTAAAATATCAGAAGG  
CAGGAGAGGAGATAGGCTTATTATGATACTAGTGAGTACATTAAGTAAAATAAAATGGAC  
CAGAAAAGAAAAGAAACCATAAATATCGTGTCAATTTTTCCCAAGATTAACCAAAAATA

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ATCTGCTTATCTTTTTGGTTGTCCTTTTAACTGTCTCCGTTTTTTTTCTTTTATTTAAAAA  
TGCACTTTTTTTCCCTTGTGAGTTATAGTCTGCTTATTTAATTACCACTTTGCAAGCCTT  
ACAAGAGAGCACAAAGTTGGCCTACATTTTTATATTTTTTAAGAAGATACTTTGAGATGCA  
TTATGAGAACTTTCAGTTCAAAGCATCAAATTGATGCCATATCCAAGGACATGCCAAATG  
CTGATTCTGTCAGGCACCTGAATGTCAGGCATTGAGACATAGGGAAGGAATGGTTTGTACT  
AATACAGACGTACAGATACTTTCTCTGAAGAGTATTTTCGAAGAGGAGCAACTGAACACT  
GGAGGAAAAGAAAATGACACTTTCTGCTTTACAGAAAAGGAAACTCATTGAGACTGGTGA  
TATCGTGATGTACCTAAAAGTCAGAAACCACATTTTCTCCTCAGAAGTAGGGACCGCTTT  
CTTACCTGTTTTAAATAAACCAAAGTATACCGTGTGAACCAAACAATCTCTTTTCAAAACA  
GGGTGCTCCTCCTGGCTTCTGGCTTCCATAAGAAGAAATGGAGAAAAATATATATATATA  
TATATATATTGTGAAAGATCAATCCATCTGCCAGAATCTAGTGGGATGGAAGTTTTTGCT  
ACATGTTATCCACCCAGGCCAGGTGGAAGTAACTGAATTATTTTTTAAATTAAGCAGTT  
CTACTCAATCACCAAGATGCTTCTGAAAATTGCATTTTATTACCATTTCAAACATTTTTT  
TAAAAATAAATACAGTTAACATAGAGTGGTTTCTTCATTCATGTGAAAAATTATTAGCCAG  
CACCAGATGCATGAGCTAATTATCTCTTTGAGTCCTTGCTTCTGTTTGCTCACAGTAAAC  
TCATTGTTTAAAAGCTTCAAGAACATTCAAGCTGTTGGTGTGTTAAAAAATGCATTGTAT  
TGATTTGTACTGGTAGTTTATGAAATTTAATTAAAACACAGGCCATGAATGGAAGGTGGT  
ATTGCACAGCTAATAAAATATGATTTGTGGATATGAA

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**FIGURE 180**

MMVRRGLLAWISRVVLLVLLCCAISVLYMLACTPKGDEEQALPRANSPTGKEGYQAV  
LQEWEEQHRNYVSSSLKRQIAQLKEELQERSEQLRNGQYQASDAAGLGLDRSPPEKTQADL  
LAF LHSQVDKAEVNAGVKLATEYA AVPFDSFTLQKVYQLETGLTRHP EEPVRKDKRDEL  
VEAIESALETLN NPAENSPNHRPYTASDFIEGIYRTERDKGTLYELTFKGDHKHEFKRLI  
LFRPFSPIMKVKNEKLN MANTLINVIVPLAKRVDKFRQFMQNFREMCIEQDGRVHLTVVY  
FGKEEINEVKGILENTSKAANFRNFTFIQLNGEFSRGKGLDVGARFWKGSNVLLFFCDVD  
IYFTSEFLNTCRLNTQPGKKVFYPVLF SQYNPGIIYGHHD AVPPLEQQLVIKKETGFWRD  
FGFGMTCQYRSDFINIGGFDLDIKGWGGEDVHLYRKYLHSNLIVVRTPVRGLFHLWHEKR  
CMDELTPEQYKCMQSKAMNEASHGQLGMLVFRHEIEAHLRKQKQKTSSKKT



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**FIGURE 181**

CGTCTCTGCGTTTCGCCATGCGTCCCGGGGCGCCAGGGCCACTCTGGCCTCTGCCCTGGGG  
GGCCCTGGCTTGGGCGGTGGGCTTCGTGAGCTCCATGGGCTCGGGGAACCCCGCGCCCGG  
TGGTGTTCGTGGCTCCAGCAGGGCCAGGAGGCCACCTGCAGCCTGGTGCTCCAGACTGA  
TGTCACCCGGGCGAGTGCTGTGCCTCCGGCAACATTGACACCGCCTGGTCCAACCTCAC  
CCACCCGGGGAACAAGATCAACCTCCTCGGCTTCTTGGGCCTTGTCCTACTGCCTTCCCTG  
CAAAGATTTCGTGCGACGGCGTGAGTGCGGGCCCGGGCAAGGCGTGCCGCATGCTGGGGGG  
CCGCCCCGCGCTGCGAGTGCGCGCCCCGACTGCTCGGGGCTCCCGGCGCGGCTGCAGGTCTG  
CGGCTCAGACGGCGCCACCTACCGCGACGAGTGCGAGCTGCGCGCCGCGCGCTGCCGCGG  
CCACCCGGACCTGAGCGTCATGTACCGGGGCGCTGCCGCAAGTCCTGTGAGCACGTGGT  
GTGCCCCGCGGCCACAGTCGTGCGTCGTGGACCAGACGGGCAGCGCCCACTGCGTGGTGTG  
TCGAGCGGCGCCCTGCCCTGTGCCCTCCAGCCCCGGCCAGGAGCTTTGCGGCAACAACAA  
CGTCACCTACATCTCCTCGTGCCACATGCGCCAGGCCACCTGCTTCTGGGCGGCTCCAT  
CGGCGTGCGCCACGCGGGCAGCTGCGCAGGCACCCCTGAGGAGCCGCCAGGTGGTGAGTC  
TGCAGAAGAGGAAGAGAACTTCGTGTGAGCGCTGCAGGACAGGCCTGGGCCTGGTGCCGA  
GGCCCCCATCATCCCCGTGTTATTTATTGCCACAGCAGAGTCTAATTTATATGCCACGGA  
CACTCCTTAGAGCCCGGATTTCGGACCACTTGGGGATCCCAAGACCTCCCTGACGATATCC  
TGGAAGGACTGAGGAAGGGAGGCCTGGGGGCGCGCTGGTGGGTGGGATAGACCTGCGTTC  
CGGACACTGAGCGCCTGATTTAGGGCCCTTCTCTAGGATGCCCCAGCCCTACCCTAAGA  
CCTATTGCCGGGGAGGATTCCACACTTCCGCTCCTTTGGGGATAAACCTATTAATTATTG  
CTACTATCAAGAGGGCTGGGCATTCTCTGCTGGTAATTCCTGAAGAGGCATGACTGCTTT  
TCTCAGCCCCAAGCCTCTAGTCTGGGTGTGTACGGAGGGTCTAGCCTGGGTGTGTACGGA  
GGGTCTAGCCTGGGTGAGTACGGAGGGTCTAGCCTGGGTGAGTACGGAGGGTCTAGCCTG  
GGTGAGTACGGAGGGTCTAGCCTGGGTGTGTATGGAGGATCTAGCCTGGGTGAGTATGGA  
GGGTCTAGCCTGGGTGAGTATGGAGGGTCTAGCCTGGGTGTGTATGGAGGGTCTAGCCTG  
GGTGAGTATGGAGGGTCTAGCCTGGGTGTGTATGGAGGGTCTAGCCTGGGTGAGTATGGA  
GGGTCTAGCCTGGGTGTGTACGGAGGGTCTAGTCTGAGTGCGTGTGGGGACCTCAGAACAA  
CTGTGACCTTAGCCCAGCAAGCCAGGCCCTTCATGAAGGCCAAGAAGGCTGCCACCATTTC  
CCTGCCAGCCCAAGAACTCCAGCTTCCCCACTGCCTCTGTGTGCCCCCTTTGCGTCTGTG  
AAGGCCATTGAGAAATGCCCAGTGTGCCCCCTGGGAAAGGGCACGGCCTGTGCTCCTGAC  
ACGGGCTGTGCTTGGCCACAGAACCACCCAGCGTCTCCCCCTGCTGCTGTCCACGTCAAGT  
CATGAGGCAACGTCGCGTGGTCTCAGACGTGGAGCAGCCAGCGGCAGCTCAGAGCAGGGC  
ACTGTGTCCGGCGGAGCCAAGTCCACTCTGGGGGAGCTCTGGCGGGGACCACGGGCCACT  
GCTCACCCACTGGCCCCGAGGGGGGTGTAGACGCCAAGACTCACGCATGTGTGACATCCG  
GAGTCTTGAGCCGGGTGTCCCAGTGGCACCACTAGGTGCCTGCTGCCTCCACAGTGGGG  
TTCACACCCAGGGCTCCTTGGTCCCCCACAACTGCCCCGGCCAGGCCTGCAGACCCAGA  
CTCCAGCCAGACCTGCCTCACCCACCAATGCAGCCGGGGCTGGCGACACCAGCCAGGTGC  
TGGTCTTGGGCCAGTTCTCCACGACGGCTCACCCCTCCCCTCCATCTGCGTTGATGCTCA  
GAATCGCCTACCTGTGCCTGCGTGTAACCAACAGCCTCAGACCAGCTATGGGGAGAGGAC  
AACACGGAGGATATCCAGCTTCCCCGGTCTGGGGTGAGGAATGTGGGGAGCTTGGGCATC  
CTCCTCCAGCCTCCTCCAGCCCCCAGGCAGTGCCCTTACCTGTGGTGCCAGAAAAGTGCC  
CCTAGGTTGGTGGGTCTACAGGAGCCTCAGCCAGGCAGCCACCCACCCTGGGGCCCTG  
CCTCACCAAGGAAATAAAGACTCAAGCCATAAAAAAA

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**FIGURE 182**

MRPGAPGPLWPLPWGALAWAVGVSSMSGGNPAPGGVCWLQQGQEATCSLVLQTDVTRAE  
CCASGNIDTAWSNLTHPGNKINLLGFLGLVHCLPCKDSCDGVCEGPGKACRMLGGRPRCE  
CAPDCSGLPARLQVCGSDGATYRDECELRAARCRGHPDLSVMYRGRCRKSCHEVVCPRPQ  
SCVVDQTGSAHCVVCRAAPCPVPSSPGQELCGNNNVTYISSCHMRQATCFLGRSIGVRHA  
GSCAGTPEEPPGGESAEFEENFV

**Important features:**

**Signal peptide:**

amino acids 1-20

**N-glycosylation sites:**

amino acids 73-77, 215-219

**Osteonectin domain proteins:**

amino acids 97-130, 169-202

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**FIGURE 183**

CACTCATTTCATTCCAAAGGGTCTCTCAAGGCAATGGTAATGTGCAAGGAGGTGATACCTA  
AATGAATGACCAAAAGAACATGCTTCTGCTTTTGTGTGTCTCCTACATTTTAGACATTTG  
TTTGTCTTCTCTTGGTAGCCTTTAAATTCTTGAAGCCCAGGACCATGTCTCACTTACCTT  
TGTGTTTTCCACTAACTAGTCTACCTCCTGGAATTGGCAGATACTCAGTGAAAGCCTGTGA  
AATAAGTGATGTCTATTTCTAGCATATTATTCTGAGATTTAATGATAGATTTAGTGATTG  
AATGAGATTTCCATTTTCAAATACAGCAAAAGCATAACTATTTTCATTTCATTTCATATTCA  
TTCAACTTCATTCTCAAAATTAGGTCCTGAGTTAACTAATAATTACCTTTGAAATGTGTG  
GGTTATTTGAGGCAATCAGGTGGTGACATTGAGCTCTCAGCCAGAGTTTGTCTTCTGGAAT  
TGATTTCAGTTCATTGCATTGATTTTGTCTCAGAGCCAAGGTTTCCCATGAAAAATC  
ATTCCCACCTTGAATTGGGCTGTGATTCTTGCTGCGTTTAAGTAAAGGAAGCCTCTTGGTT  
CTAGTTCTGCAAACTTACACACTGAACTGGGACAAGTTTGTGTTAGAGTAATGGCTGGG  
AAAAGAGGAACCTTTTCATTTTATTTCAGAAGTCAAAAACAAAGGCCTCCAGCCACCTGGA  
GATGTTTTGTGTCAGACACCAGCCTGGCTCTGTCTTTATGCCTAACAATTGAGCATCCAG  
TCTTCTTTGTGCTGGGACCATTGCTCAGCTCTGCAAGGGGAAAAGAGGGAGAAAGCCAGA  
GCTGCCAGGCTTCTTGCACTGGGGCCGGGGGAGGGTTCTTGGAAGCAGGTGCTCTCTGG  
CTTCTTGGTACGTGAGGCTCTCGGAGCTGCCTCTCCTCTGACCCTCAGGTCTCACCAG  
TTTGCTCCAGGAGTATATTGAAAACATACCCAGTGCTCTCTCAAGCACCCACTGCTTAGA  
GGGCCAGATTTCTTTTCCCTTCTTCCCTTGCAAGAGCTGGAGACTGCATCGGGCATCTGG  
TGTTTAAACTAAACAGGAAAACCTGACTAAAGGTCCACAGTGCTCATTGTGTAGACTAGCT  
GCCCTCCGATGGGTGCTCTGATTATCAGTGGTTCCAGTGCAGGGCCTGTCACTAAACAGG  
CCTCACTTCCTCCTTGGGGGCTTTCCCATGGGAGGTGTGGCTTTTTACTCTACATGGAAA  
TGACTCTCTGCAGCCACAGAACACAGTCATTTTCTGAATTATCCCAGTCTCTCATGCGCC  
CTGGATTCTCCAGATGCCTTATATCTCTTGTCAGAAAGTTGTCTAAAATTTGGTTCCAG  
CTTCCAAGCCTTGCCCTTTTGGCCTTCTGGAAGTATTTTGTGATGAGTCGTCTGTCTAT  
TATTCTCTAAAATGATTTGCTTTTTGTTTCTTTTCATTCTTATTTCCACCCACATATACA  
CACATGCTTCTTAACTTAGGGGATTACATGCCAATAAATCTATTGTTGAAAATGCACTAA  
TACTATCGCAAAGACGAAAATTCACAGGCTGAACCGTTGTAAGTCCATATGCTCCTCAAC  
TTACATGTGTGATGGAGTTATGCCCAAATAAGTCCATCGTCAAGTTGAAAATCAAATC  
AAGCCATCTTAGGTTGAGGACCATTGTGTTGTACCTCCAAAGATGTCATATCTTTAAACA  
TACTCCCTAGCTTTTCTTTTACTTTTATTTTGAAGTAATTATAGAATCACAGAAAGTT  
GCAAAAAA

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## FIGURE 184

MGALIIISGSSAGPVTQASLPPWGLSHGRCGFLLYMENTLCSHRTQSFSELSQSLMRPGF  
LQMPYISCAKLSKIWFPAKPCLLAFLEVFLMSRLSLFSKMICFLFLSFLFPPHIYTHAS

**Important features of the protein:**

**Signal peptide:**

amino acids 1-41

**Transmembrane domain:**

amino acids 88-107

**Casein kinase II phosphorylation site:**

amino acids 47-50

**N-myristoylation site:**

amino acids 24-29

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**FIGURE 185**

AACTCAAACCTCCTCTCTCTGGGAAAACGCGGTGCTTGCTCCTCCCGGAGTGGCCTTGGCA  
GGGTGTTGGAGCCCTCGGTCTGCCCCGTCCGGTCTCTGGGGCCAAGGCTGGGTTTCCCTC  
ATGTATGGCAAGAGCTCTACTCGTGCGGTGCTTCTTCTCCTTGGCATACAGCTCACAGCT  
CTTTGGCCTATAGCAGCTGTGGAAATTTATACCTCCCGGGTGCTGGAGGCTGTTAATGGG  
ACAGATGCTCGGTTAAAATGCACCTTTCTCCAGCTTTGCCCCCTGTGGGTGATGCTCTAACA  
GTGACCTGGAATTTTCGTCTCTAGACGGGGGACCTGAGCAGTTTGTATTCTACTACCAC  
ATAGATCCCTTCCAACCCATGAGTGGGCGGTTTAAGGACCGGGTGTCTTGGGATGGGAAT  
CCTGAGCGGTACGATGCCTCCATCCTTCTCTGGAACTGCAGTTCGACGACAATGGGACA  
TACACCTGCCAGGTGAAGAACCACCTGATGTTGATGGGGTGATAGGGGAGATCCGGCTC  
AGCGTCGTGCACACTGTACGCTTCTCTGAGATCCACTTCCTGGCTCTGGCCATTGGCTCT  
GCCTGTGCACTGATGATCATAATAGTAATTGTAGTGGTCCTCTTCCAGCATTACCGGAAA  
AAGCGATGGGCCGAAAGAGCTCATAAAGTGGTGGAGATAAAATCAAAGAAGAGGAAAGG  
CTCAACCAAGAGAAAAAGGTCTCTGTTTATTTAGAAGACACAGACTTAACAATTTTAGATG  
GAAGCTGAGATGATTTCCAAGAACAAAGAACCTAGTATTTCTTGAAGTTAATGGAACTT  
TTCTTTGGCTTTTCCAGTTGTGACCCGTTTCCAACCAGTTCTGCAGCATATTAGATTCT  
AGACAAGCAACACCCCTCTGGAGCCAGCACAGTGCTCCTCCATATCACCAGTCATACACA  
GCCTCATTATTAAGGTCTTATTTAATTTTCAAGAGTGTAATTTTTTCAAGTGCTCATTAGG  
TTTTATAACAAGAAGCTACATTTTGGCCCTTAAGACACTACTTACAGTGTTATGACTTG  
TATACACATATATTGGTATCAAAGGGGATAAAAGCCAATTTGTCTGTTACATTTCTTTTC  
ACGTATTTCTTTTAGCAGCACTTCTGCTACTAAAGTTAATGTGTTTACTCTCTTTCCTTC  
CCACATTCTCAATTAAAAGGTGAGCTAAGCCTCCTCGGTGTTTCTGATTAACAGTAAATC  
CTAAATTCAAACGTGTTAAATGACATTTTATTTTATGTCTCTCCTTAACATATGAGACAC  
ATCTTGTTTTACTGAATTTCTTTCAATATTCCAGGTGATAGATTTTTGTGCG

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## FIGURE 186

MYGKSSTRAVLLLLGIQLTALWPAAVEIYTSRVLEAVNGTDARLKCTFSSFAPVGDALT  
VTWNFRPLDGGPEQFVFYHIDPFQPMGRFKDRVSWDGNPERYDASILLWKLQFDDNGT  
YTCQVKNPPDVGVIQIRLSVVHTVRFSEIHFLALAIGSACALMIIIVIVVVLFFQHYRK  
KRWAERAHKVVEIKSKEEERLNQEKVSVYLETD

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**FIGURE 187**

GCATTTTGTCTGTGCTCCCTGATCTTCAGGTCACCACCATGAAGTTCTTAGCAGTCCTG  
GTA CTCTTGGGAGTTTCCATCTTTCTGGTCTCTGCCCAGAATCCGACAACAGCTGCTCCA  
GCTGACACGTATCCAGCTACTGGTCCTGCTGATGATGAAGCCCCTGATGCTGAAACCACT  
GCTGCTGCAACCACTGCGACCACTGCTGCTCCTACCACTGCAACCACCGCTGCTTCTACC  
ACTGCTCGTAAAGACATTCCAGTTTTACCCAAATGGGTTGGGGATCTCCCGAATGGTAGA  
GTGTGTCCCTGAGATGGAATCAGCTTGAGTCTTCTGCAATTGGTCACAAC TATTCATGCT  
TCCTGTGATTT CATCCA ACTACTTACCTTGCCTACGATATCCCCTTTATCTCTAATCAGT  
TTATTTTCTTTCAAATAAAAAATAACTATGAGCAACATAAAAAAAAAAAAAA

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## FIGURE 188

MKFLAVLVLLGVSI FLVSAQNPTTAAPADTYPATGPADDEAPDAETTAAATTATTAAPT  
ATTAASTTARKDIPVLPKWVGDLPNGRVCP



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**FIGURE 189**

GAGCGAACATGGCAGCGCGTTGGCGGTTTTGGTGTGTCTCTGTGACCATGGTGGTGGCGC  
TGCTCATCGTTTTGCGACGTTCCCTCAGCCTCTGCCCAAAGAAAGAAGGAGATGGTGTAT  
CTGAAAAGGTTAGTCAGCTGATGGAATGGACTAACAAAAGACCTGTAATAAGAATGAATG  
GAGACAAGTTCCGTCGCCTTGTGAAAGCCCCACCGAGAAATTACTCCGTTATCGTCATGT  
TCACTGCTCTCCAACATGCATAGACAGTGTGTGCTTTGCAAGCAAGCTGATGAAGAATTCC  
AGATCCTGGCAAACCTCCTGGCGATACTCCAGTGCATTACCAACAGGATATTTTTTGCCA  
TGGTGGATTTTGATGAAGGCTCTGATGTATTTAGATGCTAAACATGAATTCAGCTCCAA  
CTTTCATCAACTTTCTTGCAAAAGGGAAACCCAAACGGGGTGATACATATGAGTTACAGG  
TGCGGGGTTTTTCAGCTGAGCAGATTGCCCGGTGGATCGCCGACAGAACTGATGTCAATA  
TTAGAGTGAATTAGACCCCCAAATTATGCTGGTCCCCTTATGTTGGGATTGCTTTTGGCTG  
TTATTGGTGGACTTGTGTATCTTCGAAGAAGTAATATGGAATTTCTCTTTAATAAACTG  
GATGGGCTTTTGACAGCTTGTGTATTTGTGCTTGCTATGACATCTGGTCAAATGTGGAACC  
ATATAAGAGGACCACCATATGCCCATAGAATCCCCACACGGGACATGTGAATTATATCC  
ATGGAAGCAGTCAAGCCCAGTTGTAGCTGAAACACACATTGTTCTTCTGTTAATGGTG  
GAGTTACCTTAGGAATGGTGTCTTTATGTGAAGCTGCTACCTCTGACATGGATATTGGAA  
AGCGAAAGATAATGTGTGTGGCTGGTATTGGACTTGTGTATTATTCTTCAGTTGGATGC  
TCTCTATTTTTAGATCTAAATATCATGGCTACCCATACAGCTTTCTGATGAGTTAAAAAG  
GTCCCAGAGATATATAGACACTGGAGTACTGGAAATTGAAAAACGAAAATCGTGTGTGT  
TGAAAAGAAGAATGCAACTTGTATATTTTGTATTACCTCTTTTTTTCAAGTGATTTAAAT  
AGTTAATCATTTAACCAGAAAGATGTGTAGTGCCTTAACAAGCAATCCTCTGTCAAAAT  
CTGAGGTATTTGAAAATAATTATCCTCTTAACCTTCTCTTCCCAGTGAACCTTTATGGAAC  
ATTTAATTTAGTACAATTAAGTATATTATAAAAAATTGTAAACTACTACTTTGTTTTAGT  
TAGAACAAAGCTCAAACTACTTTAGTTAACTTGGTCATCTGATTTTATATTGCCTTATC  
CAAAGATGGGGAAAGTAAGTCTTGACCAGGTGTTCCACATATGCCTGTTACAGATAACT  
ACATTAGGAATTCATTCTTAGCTTCTTCATCTTTGTGTGGATGTGTATACTTTACGCATC  
TTTCTTTTTGAGTAGAGAAATTATGTGTGTATGTGGTCTTCTGAAAATGGAACACCATT  
CTTCAGAGCACACGTCTAGCCCTCAGCAAGACAGTTGTTTCTCCTCCTCCTTGCATATTT  
CCTACTGCGCTCCAGCCTGAGTGATAGAGTGAGACTCTGTCTCAAAAAAAGTATCTCTA  
AATACAGGATTATAATTTCTGCTTGAGTATGGTGTAACTACCTTGTATTTAGAAAGATT  
TCAGATTCAATCCATCTCCTTAGTTTTCTTTAAGGTGACCCATCTGTGATAAAAATATA  
GCTTAGTGCTAAAATCAGTGTAACCTATACATGGCCTAAAATGTTTCTACAAATTAGAGT  
TTGTCACTTATTCCATTTGTACCTAAGAGAAAAATAGGCTCAGTTAGAAAAGGACTCCCT  
GGCCAGGCGCAGTGACTTACGCCTGTAATCTCAGCACTTTGGGAGGCCAAGGCAGGCAGA  
TCACGAGGTGAGGAGTTCGAGACCATCCTGGCCAAACATGGTGAAACCCCGTCTCTACTAA  
AAATATAAAAAATTAGCTGGGTGTGGTGGCAGGAGCCTGTAATCCCAGCTACACAGGAGGC  
TGAGGCACGAGAATCACTTGAACCTCAGGAGATGGAGGTTTCAGTGAGCCGAGATCACGCC  
ACTGCACTCCAGCCTGGCAACAGAGCGAGACTCCATCTCAAAAAAAAAAAAAA

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**FIGURE 190**

MAARWRFWCVSVTMVVALLIVCDVPSASAQRKKEMVLSEKVSQLMEWTKRPFVIRMNGDK  
FRRLVKAPPRNYSVIVMFTALQLHRQCVCKQADEEFQILANSWRYSSAFTNRIFFAMVD  
FDEGSDVFQMLNMNSAPTFINFPAGKPKRGDTYELQVRGFSAEQIARWIADRTDVNIRV  
IRPPNYAGPLMLGLLLAVIGGLVYLRRSNMEFLFNKTGWAFALCFVLAMTSGQMWNHIR  
GPPYAHKNPHTGHVNYIHGSSQAQFVAETHIVLLFNNGVTLGMVLLCEAATSDMDIGKRK  
IMCVAGIGLVVLFPSWMLSI FRSKYHGYPYSFLMS

**Signal peptide:**  
amino acids 1-29

**Transmembrane domains:**  
amino acids 183-205, 217-237, 217-287, 301-321

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**FIGURE 191**

GAGAGAAGTCAGCCTGGCAGAGAGACTCTGAAATGAGGGATTAGAGGTGTTCAAGGAGCA  
AGAGCTTCAGCCTGAAGACAAGGGAGCAGTCCCTGAAGACGCTTCTACTGAGAGGTCTGC  
CATGGCCTCTCTTGGCCTCCAACTTGTGGGCTACATCCTAGGCCTTCTGGGGCTTTTGGG  
CACACTGGTTGCCATGCTGCTCCCCAGCTGGAAAACAAGTTCTTATGTCGGTGCCAGCAT  
TGTGACAGCAGTTGGCTTCTCCAAGGGCCTCTGGATGGAATGTGCCACACACAGCACAGG  
CATCACCCAGTGTGACATCTATAGCACCCCTTCTGGGCCTGCCCCGTGACATCCAGGCTGC  
CCAGGCCATGATGGTGACATCCAGTGCAATCTCCTCCCTGGCCTGCATTATCTCTGTGGT  
GGGCATGAGATGCACAGTCTTCTGCCAGGAATCCCGAGCCAAAGACAGAGTGGCGGTAGC  
AGGTGGAGTCTTTTTCATCCTTGGAGGCCTCCTGGGATTCATTCCCTGTTGCCCTGGAATCT  
TCATGGGATCCTACGGGACTTCTACTCACCACTGGTGCCTGACAGCATGAAATTTGAGAT  
TGGAGAGGCTCTTTACTTGGGCATTATTTCTTCCCTGTTCTCCCTGATAGCTGGAATCAT  
CCTCTGCTTTTCTTGCTCATCCCAGAGAAATCGCTCCAACTACTACGATGCCTACCAAGC  
CCAACCTCTTGCCACAAGGAGCTCTCCAAGGCCTGGTCAACCTCCCAAAGTCAAGAGTGA  
GTTCAATTCTACAGCCTGACAGGGTATGTGTGAAGAACCAGGGGCCAGAGCTGGGGGGT  
GGCTGGGTCTGTGAAAAACAGTGGACAGCACCCCGAGGGCCACAGGTGAGGGACACTACC  
ACTGGATCGTGTGAGAAGGTGCTGCTGAGGATAGACTGACTTTGGCCATTGGATTGAGCA  
AAGGCAGAAATGGGGGCTAGTGTAACAGCATGCAGGTTGAATTGCCAAGGATGCTCGCCA  
TGCCAGCCTTTCTGTTTTCTCACCTTGCTGCTCCCCTGCCCTAAGTCCCCAACCCCTCAA  
CTTGAAACCCCATTCCTTAAGCCAGGACTCAGAGGATCCCTTTGCCCTCTGGTTTACCT  
GGGACTCCATCCCCAAACCCACTAATCACATCCCCTGACTGACCCTCTGTGATCAAAGA  
CCCTCTCTCTGGCTGAGGTTGGCTCTTAGCTCATTGCTGGGGATGGGAAGGAGAAGCAGT  
GGCTTTTGTGGGCATTGCTCTAACCTACTTCTCAAGCTTCCCTCCAAAGAACTGATTGG  
CCCTGGAACCTCCATCCCCTCTTGTTATGACTCCACAGTGTCCAGACTAATTTGTGCAT  
GAACTGAAATAAAACCATCCTACGGTATCCAGGGAACAGAAAGCAGGATGCAGGATGGGA  
GGACAGGAAGGCAGCCTGGGACATTTAAAAAATA

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**FIGURE 192**

MASLGLQLVGYILGLLGTLVAMLLPSWKTSSYVGASIVTAVGFSKGLWMECATHSTG  
ITQCDIYSTLLGLPADIQAAQAMMVTSSAISSLACIISVVGMRCTVFCQESRAKDRVAVA  
GGVFFILGLLGFIPVAWNLHGILRDFYSPLVPDSMKFEIGEALYLGIISSLFSLIAGII  
LCFSCSSQRNRSNYYDAYQAQPLATRSSPRPGQPPKVKSEFNSYSLTGYV

**Important features of the protein:**

**Signal peptide:**

amino acids 1-24

**Transmembrane domains:**

amino acids 82-102, 117-140, 163-182

**N-glycosylation site:**

amino acids 190-193

**PMP-22 / EMP / MP20 family proteins:**

amino acids 46-59

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**FIGURE 193**

CTCCACTGCAACCACCCAGAGCCATGGCTCCCCGAGGCTGCATCGTAGCTGTCTTTGCCA  
TTTTCTGCATCTCCAGGCTCCTCTGCTCACACGGAGCCCCAGTGGCCCCCATGACTCCTT  
ACCTGATGCTGTGCCAGCCACACAAGAGATGTGGGGACAAGTTCTACGACCCCCTGCAGC  
ACTGTTGCTATGATGATGCCGTCGTGCCCTTGGCCAGGACCCAGACGTGTGGAAACTGCA  
CCTTCAGAGTCTGCTTTGAGCAGTGCTGCCCCTGGACCTTCATGGTGAAGCTGATAAACC  
AGAACTGCGACTCAGCCCGGACCTCGGATGACAGGCTTTGTGCGAGTGTGAGCTAATGGA  
ACATCAGGGGAACGATGACTCCTGGATTCTCCTTCCTGGGTGGGCCTGGAGAAAGAGGCT  
GGTGTTACCTGAGATCTGGGATGCTGAGTGGCTGTTTGGGGGCCAGAGAAACACACACTC  
AACTGCCCACTTCATTCTGTGACCTGTCTGAGGCCACCCCTGCAGCTGCCCTGAGGAGGC  
CCACAGGTCCCCTTCTAGAATTCTGGACAGCATGAGATGCGTGTGCTGATGGGGGCCAG  
GGACTCTGAACCCTCCTGATGACCCCTATGGCCAAACATCAACCCGGCACCACCCAAGGC  
TGGCTGGGGAACCCTTACCCTTCTGTGAGATTTTCCATCATCTCAAGTTCTCTTCTATC  
CAGGAGCAAAGCACAGGATCATAATAAATTTATGTACTTTATAAATGAAAA

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## FIGURE 194

MAPRGCIVAVFAIFCISRLLC SHGAPVAPMTPYLMLCQPHKRCGDKFYDPLQHCCYDDAV  
VPLARTQTCGNCTFRVCFEQCCPWTFMVKLINQNCDSARTSDDRLCRSVS

**Signal peptide:**  
amino acids 1-24

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**FIGURE 195**

CATTTCCAACAAGAGCACTGGCCAAGTCAGCTTCTTCTGAGAGAGTCTCTAGAAGACATG  
ATGCTACACTCAGCTTTGGGTCTCTGCCTCTTACTCGTCACAGTTTCTTCCAACCTTGCC  
ATTGCAATAAAAAAGGAAAAGAGGCCTCCTCAGACACTCTCAAGAGGATGGGGAGATGAC  
ATCACTTGGGTACAACTTATGAAGAAGGTCTCTTTTATGCTCAAAAAAGTAAGAAGCCA  
TTAATGGTTATTATCACCTGGAGGATTGTCAATACTCTCAAGCACTAAAGAAAGTATTT  
GCCCAAATGAAGAAATACAAGAAATGGCTCAGAATAAGTTCATCATGCTAAACCTTATG  
CATGAAACCACTGATAAGAATTTATCACCTGATGGGCAATATGTGCCTAGAATCATGTTT  
GTAGACCCTTCTTTAACAGTTAGAGCTGACATAGCTGGAAGATACTCTAACAGATTGTAC  
ACATATGAGCCTCGGGATTTACCCCTATTGATAGAAAACATGAAGAAAGCATTAAGACTT  
ATTCAGTCAGAGCTATAAGAGATGATGGAAAAAGCCTTCACTTCAAAGAAGTCAAATTT  
CATGAAGAAAACCTCTGGCACATTGACAAATACTAAATGTGCAAGTATATAGATTTTGTA  
ATATTACTATTTAGTTTTTTTAAATGTGTTTGCAATAGTCTTATTAAAATAAATGTTTTT  
AAATCTGA

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**FIGURE 196**

MMLHSALGLCLLLVTVSSNLAIKKEKRPPQTL SRGWGDDITWVQTYEEGLFYAQKSKK  
PLMVIHHLEDCQYSQALKKVFAQNEEIQEMAQNKFIMLNLMHETTDKNLSPDGQYVPRIM  
FVDPSLTVRADIAGRYSNRLYTYEPRDLPLLIENMKKALRLIQSEL

**Important features:**

**Signal peptide:**

amino acids 1-23

**N-myristoylation site:**

amino acids 51-57



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**FIGURE 197**

GGGGGCGGGTGCCTGGAGCACGGCGCTGGGGCCGCCCGCAGCGCTCACTCGCTCGCACTC  
AGTCGCGGGAGGCTTCCCCGCGCCGGCCGCGTCCCGCCCGCTCCCCGGCACCAGAAGTTC  
CTCTGCGCGTCCGACGGCGACATGGGCGTCCCCACGGCCCTGGAGGCCGGCAGCTGGCGC  
TGGGGATCCCTGCTCTTCGCTCTCTTCCTGGCTGCGTCCCTAGGTCCGGTGGCAGCCTTC  
AAGGTGCGCCACGCCGTATTCCCTGTATGTCTGTCCCAGGGGGCAGAACGTCACCCTCACC  
TGCAGGCTCTTGGGCCCTGTGGACAAAGGGCACGATGTGACCTTCTACAAGACGTGGTAC  
CGCAGCTCGAGGGGCGAGGTGCAGACCTGCTCAGAGCGCCGGCCCATCCGCAACCTCACG  
TTCCAGGACCTTCACCTGCACCATGGAGGCCACCAGGCTGCCAACACCAGCCACGACCTG  
GCTCAGCGCCACGGGCTGGAGTCGGCCCTCCGACCACCATGGCAACTTCTCCATCACCATG  
CGCAACCTGACCCTGCTGGATAGCGGCCTCTACTGCTGCCTGGTGGTGGAGATCAGGCAC  
CACCCTCGGAGCACAGGGTCCATGGTGCCATGGAGCTGCAGGTGCAGACAGGCAAAGAT  
GCACCATCCAACGTGTGTGGTGTACCCATCCTCCTCCAGGATAGTGAACCATCACGGCT  
GCAGCCCTGGCTACGGGTGCCTGCATCGTAGGAATCCTCTGCCTCCCCCTCATCCTGCTC  
CTGGTCTACAAGCAAAGGCAGGCAGCCTCCAACCGCCGTGCCAGGAGCTGGTGC GGATG  
GACAGCAACATTCAAGGGATTGAAAACCCCGGCTTTGAAGCCTCACCACCTGCCCAGGGG  
ATACCCGAGGCCAAAGTCAGGCACCCCTGTCTATGTGGCCAGCGGCAGCCTTCTGAG  
TCTGGGCGGCATCTGCTTTCGGAGCCAGCACCCCTGTCTCCTCCAGGCCCGGAGAC  
GTCTTCTTCCCATCCCTGGACCTGTCCCTGACTCTCCAACTTTGAGGTCATCTAGCCC  
AGCTGGGGGACAGTGGGCTGTTGTGGCTGGGTCTGGGGCAGGTGCATTTGAGCCAGGGCT  
GGCTCTGTGAGTGGCCTCCTTGGCCTCGGCCCTGGTTCCCTCCCTCCTGCTCTGGGCTCA  
GATACTGTGACATCCCAGAAGCCCAGCCCTCAACCCCTCTGGATGCTACATGGGGATGC  
TGGACGGCTCAGCCCCTGTTCCAAGGATTTTGGGGTGTGAGATTCTCCCCTAGAGACCT  
GAAATTCACCAGCTACAGATGCCAAATGACTTACATCTTAAGAAAGTCTCAGAACGTCCAG  
CCCTTCAGCAGCTCTCGTTCTGAGACATGAGCCTTGGGATGTGGCAGCATCAGTGGGACA  
AGATGGACACTGGGCCACCCTCCCAGGCACCAGACACAGGGCACGGTGGAGAGACTTCTC  
CCCCGTGGCCGCTTGGCTCCCCCGTTTTGCCCCAGGCTGCTCTTCTGTGAGACTTCTC  
TTTGTACCACAGTGGCTCTGGGGCCAGGCCTGCCTGCCCCTGGCCATCGCCACCTTCCC  
CAGCTGCCTCCTACCAGCAGTTTCTCTGAAGATCTGTCAACAGGTAAAGTCAATCTGGGG  
CTTCCACTGCCTGCATTCCAGTCCCCAGAGCTTGGTGGTCCCGAAACGGGAAGTACATAT  
TGGGGCATGGTGGCCTCCGTGAGCAAATGGTGTCTTGGGCAATCTGAGGCCAGGACAGAT  
GTTGCCCCACCCACTGGAGATGGTGTGAGGGAGGTGGGTGGGGCCTTCTGGGAAGGTGA  
GTGGAGAGGGGCACCTGCCCCCGCCCTCCCCATCCCCCTACTCCCACTGCTCAGCGCGGG  
CCATTGCAAGGGTGCCACACAATGTCTGTCCACCCTGGGACACTTCTGAGTATGAAGCG  
GGATGCTATTAAAACTACATGGGGAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA  
AAGA

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**FIGURE 198**

MGVPTALEAGSWRWGSLLFALFLAASLGPVAAFKVATPYSLYVCPEGQNVTLTCRLLGPV  
DKGHDVTFYKTYWRSSRGEVQTCSERRPIRNLTFQDLHLHHGGHQAANTSHDLAQRHGLE  
SASDHHGNFSITMRNLTLDSGLYCCLVVEIRHHHSEHRVHGAMELQVQTGKDAPSNCVV  
YPSSSQDSENITAAALATGACIVGILCLPLILLLVYKQRQAASNRAQELVRMDSNIQGI  
ENPGFEASPPAQGIPEAKVRHPLSYVAQRQPSESGRHLLSEPSTPLSPPGPGDVFFPSLD  
PVPDSPNFEVI

**Signal peptide:**  
amino acids 1-28

**Transmembrane domain:**  
amino acids 190-216

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**FIGURE 199**

CTAGCCTGCGCCAAGGGGTAGTGAGACCGCGCGGCAACAGCTTGCGGCTGCGGGGAGCTC  
CCGTGGGCGCTCCGCTGGCTGTGCAGGCGGCCATGGATTCCTTGCGGAAAATGCTGATCT  
CAGTCGCAATGCTGGGCGCAGGGGCTGGCGTGGGCTACGCGCTCCTCGTTATCGTGACCC  
CGGGAGAGCGGCGGAAGCAGGAAATGCTAAAGGAGATGCCACTGCAGGACCCAAGGAGCA  
GGGAGGAGGCGGCCAGGACCCAGCAGCTATTGCTGGCCACTCTGCAGGAGGCAGCGACCA  
CGCAGGAGAACGTGGCCTGGAGGAAGAACTGGATGGTTGGCGGCGAAGGCGGCGCCAGCG  
GGAGGTCACCGTGAGACCGGACTTGCCCTCCGTGGGCGCCGGACCTTGGCTTGGGCGCAGG  
AATCCGAGGCAGCCTTTCTCCTTCGTGGGCCCAGCGGAGAGTCCGGACCGAGATACCATG  
CCAGGACTCTCCGGGGTCTGTGAGCTGCCGTCCGGTGAGCACGTTTCCCCCAACCCTG  
GACTGACTGCTTTAAGGTCCGCAAGGCGGGCCAGGGCCGAGACGCGAGTCGGATGTGGTG  
AACTGAAAGAACCAATAAAATCATGTTCTCCAAAAAAAAAAAAAAAAAAAAAAAAAAAAA  
AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA

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## FIGURE 200

MDSLRLKMLISVAMLGAGAGVGYALLVIVTPGERRKQEMLKEMPLQDPRSREEAARTQQLL  
LATLQEAATTQENVAWRKNWMVGEGGASGRSP

Signal peptide:  
amino acids 1-18

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**FIGURE 201**

GACAGCTGTGTCTCGATGGAGTAGACTCTCAGAACAGCGCAGTTTGGCCCTCCGCTCACGC  
AGAGCCTCTCCGTGGCTTCCGCACCTTGAGCATTAGGCCAGTTCTCCTCTTCTCTCTAAT  
CCATCCGTCACCTCTCCTGTATCCGTTTCCATGCCGTGAGGTCCATTACAGAACACAT  
CCATGGCTCTCATGCTCAGTTTGGTTCTGAGTCTCCTCAAGCTGGGATCAGGGCAGTGGC  
AGGTGTTTGGGCCAGACAAGCCTGTCCAGGCCCTTGGTGGGGGAGGACGCAGCATTCTCCT  
GTTTCCTGTCTCCTAAGACCAATGCAGAGGCCATGGAAGTGCGGTTCTTCAGGGGCCAGT  
TCTCTAGCGTGGTCCACCTCTACAGGGACGGGAAGGACCAGCCATTTATGCAGATGCCAC  
AGTATCAAGGCAGGACAAAACCTGGTGAAGGATTCTATTGCGGAGGGGGCGCATCTCTCTGA  
GGCTGGAACACATTACTGTGTTGGATGCTGGCCTCTATGGGTGCAGGATTAGTTCCCAGT  
CTTACTACCAGAAGGCCATCTGGGAGCTACAGGTGTGAGCACTGGGCTCAGTTCCTCTCA  
TTTCCATCACGGGATATGTTGATAGAGACATCCAGCTACTCTGTGAGTCCCTCGGGCTGGT  
TCCCCCGGGCCACAGCGAAGTGGAAGGTCCACAAGGACAGGATTTGTCCACAGACTCCA  
GGACAAACAGAGACATGCATGGCCTGTTTGATGTGGAGATCTCTCTGACCGTCCAAGAGA  
ACGCCGGGAGCATATCCTGTTCCATGCGGCATGCTCATCTGAGCCGAGAGGTGGAATCCA  
GGGTACAGATAGGAGATACCTTTTTTCGAGCCTATATCGTGGCACCTGGCTACCAAAGTAC  
TGGGAATACTCTGCTGTGGCCTATTTTTTGGCATTTGTTGGACTGAAGATTTTCTTCTCCA  
AATTCCAGTGGAACATCCAGGCGGAACCTGGACTGGAGAAGAAAGCACGGACAGGCAGAAT  
TGAGAGACGCCCCGGAACACGCAGTGGAGGTGACTCTGGATCCAGAGACGGCTCACCCGA  
AGCTCTGCGTTTCTGATCTGAAAACCTGTAAACCCATAGAAAAGCTCCCCAGGAGGTGCCTC  
ACTCTGAGAAGAGATTTACAAGGAAGAGTGTGGTGGCTTCTCAGAGTTTCCAAGCAGGGA  
AACATTACTGGGAGGTGGACGGAGGACACAATAAAAGGTGGCGCGTGGGAGTGTGCCGGG  
ATGATGTGGACAGGAGGAAGGAGTACGTGACTTTGTCTCCCGATCATGGGTACTGGGTCC  
TCAGACTGAATGGAGAACATTTGTATTTACATTAAATCCCCGTTTATCAGCGTCTTCC  
CCAGGACCCCCACCTACAAAATAGGGGTCTTCTGGACTATGAGTGTGGGACCATCTCCT  
TCTTCAACATAAATGACCAGTCCCTTATTTATACCCTGACATGTGGTGTGAAGGCTTAT  
TGAGGCCCTACATTGAGTATCCGTCTATAATGAGCAAAATGGAACCTCCCATAGTCATCT  
GCCCAGTCACCCAGGAATCAGAGAAAGAGGCCTCTTGGCAAAGGGCCTCTGCAATCCCAG  
AGACAAGCAACAGTGAGTCCTCCTCACAGGCAACCACGCCCTTCTCCCCAGGGGTGAAA  
TGTAAGGATGAATCACATCCACATTCTTCTTTAGGGATATTAAGGTCTCTCTCCAGATC  
CAAAGTCCCGCAGCAGCCGGCCAAGGTGGCTTCCAGATGAAGGGGGACTGGCCTGTCCAC  
ATGGGAGTCAGGTGTCTATGGCTGCCCTGAGCTGGGAGGGAAGAAGGTGACATTACATTT  
AGTTTGCTCTCACTCCATCTGGCTAAGTGATCTTGAAATACCACCTCTCAGGTGAAGAAC  
CGTCAGGAATTTCCATCTCACAGGCTGTGGTGTAGATTAAGTAGACAAGGAATGTGAATA  
ATGCTTAGATCTTATTGATGACAGAGTGTATCCTAATGGTTTGTTCATTATATTACACTT  
TCAGTAAAAAAA

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**FIGURE 202**

MALMLSLVLSLLKLGSGQWQVFGPDKPVQALVGEDAAFSCLSPKTNAEAMEVRFFRGQF  
SSVHLYRDGKDQPFMQMPQYQGRTKLVKDSIAEGRISLRLENITVLDAGLYGCRISQS  
YYQKAIWELQVSALGSVPLISITGYVDRDIQLLCQSSGWFPRTAKWKGPQGDLSTDSR  
TNRDMHGLFDVEISLTVQENAGSISCSMRHAHLSREVESRVQIGDTFFEPISWHLATKVL  
GILCCGLFFGIVGLKIFFSKFQWKIQAEWDWRRKHGQAEIRDARKHAVEVTLDPETAHPK  
LCVSDLKTVTHRKAPOEVPHSEKRFTRKSVVASQSFQAGKHYWEVDGGHNKRWRVGVCRD  
DVDRRKEYVTLSPDHGYWVLRNLNGEHLFTLNPRFISVFPRTPTKIGVFLDYECGTISF  
FNINDQSLIYTLTCRFEGLLRPYIEYPSYNEQNGTPIVICPVTQESEKEASWQRASAIPE  
TSNSESSSQATTPFLPRGEM

**Signal peptide:**  
amino acids 1-17

**Transmembrane domain:**  
amino acids 239-255

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**FIGURE 203**

TGCGGCGCAGTGTAGACCTGGGAGGATGGGCGGCCTGCTGCTGGCTGCTTTTCTGGCTTT  
GGTCTCGGTGCCCAGGGCCCAGGCCGTGTGGTTGGGAAGACTGGACCCTGAGCAGCTTCT  
TGGGCCCTGGTACGTGCTTGCGGTGGCCTCCCGGGAAAAGGGCTTTGCCATGGAGAAGGA  
CATGAAGAACGTCGTGGGGGTGGTGGTGACCCTCACTCCAGAAAACAACCTGCGGACGCT  
GTCCTCTCAGCACGGGCTGGGAGGGTGTGACCAGAGTGTATGGACCTGATAAAGCGAAA  
CTCCGGATGGGTGTTTGAGAATCCCTCAATAGGCGTGCTGGAGCTCTGGGTGCTGGCCAC  
CAACTTCAGAGACTATGCCATCATCTTCACTCAGCTGGAGTTCGGGGACGAGCCCTTCAA  
CACCGTGGAGCTGTACAGTCTGACGGAGACAGCCAGCCAGGAGGCCATGGGGCTCTTCAC  
CAAGTGGAGCAGGAGCCTGGGCTTCCTGTACAGTAGCAGGCCCAGCTGCAGAAGGACCT  
CACCTGTGCTCACAAGATCCTTCTGTGAGTGCTGCGTCCCCAGTAGGGATGGCGCCCACA  
GGGTCTGTGACCTCGGCCAGTGTCCACCCACCTCGCTCAGCGGCTCCCGGGGCCAGCA  
CCAGCTCAGAATAAAGCGATTCCACAGCA

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## FIGURE 204

MGGLLLAFLALVSVPRQA VWLGRLDPEQLLGPWYVLAVASREKGFAMEKDMKNVVG VV  
VTLT PENNLR TLSSQHGLGGCDQSVMDLIKRN SGWVFENPSIGVLELWVLATNFRDYAI I  
FTQLEFGDEPFNTVELYSLTETASQEAMGLFTKWSRSLGFLSQ

Signal peptide:  
amino acids 1-20



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**FIGURE 205**

GACGCCCAGTGACCTGCCGAGGTCGGCAGCACAGAGCTCTGGAGATGAAGACCCTGTTCC  
TGGGTGTCACGCTCGGCCTGGCCGCTGCCCTGTCCTTCACCCTGGAGGAGGAGGATATCA  
CAGGGACCTGGTACGTGAAGGCCATGGTGGTCGATAAGGACTTTCGGGAGGACAGGAGGC  
CCAGGAAGGTGTCCCCAGTGAAGGTGACAGCCCTGGGCGGTGGGAAGTTGGAAGCCACGT  
TCACCTTCATGAGGGAGGATCGGTGCATCCAGAAGAAAATCCTGATGCGGAAGACGGAGG  
AGCCTGGCAAATACAGCGCCTATGGGGGCAGGAAGCTCATGTACCTGCAGGAGCTGCCCCA  
GGAGGGACCACTACATCTTTTACTGCAAAGACCAGCACCATGGGGGCCTGCTCCACATGG  
GAAAGCTTGTGGGTAGGAATTCTGATACCAACCGGGAGGCCCTGGAAGAATTTAAGAAAT  
TGGTGCAGCGCAAGGGACTCTCGGAGGAGGACATTTTCACGCCCCCTGCAGACGGGAAGCT  
GCGTTCCCGAACACTAGGCAGCCCCCGGGTCTGCACCTCCAGAGCCCACCCTACCACCAG  
ACACAGAGCCCGGACCACCTGGACCTACCCTCCAGCCATGACCCTTCCCTGCTCCCAACC  
ACCTGACTCCAAATAAAGTCCTTTTCCCCCAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA  
AAAAAAAAAAAAAAAAAAAAA

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## FIGURE 206

MKTLFLGVTLGLAAALSFTLEEEDITGTWYVKAMVVDKDFPEDRRPRKVS PVKVTALGGG  
KLEATFTFMREDRCIQKKILMRKTEEPGKYSAYGGRKLMYLQELPRRDHYIFYCKDQHHG  
GLLHMGKLVGRNSDTNREALEEFKKLVQRKGLSEEDIFTPLQTGSCVPEH

**Important features:**

**Signal peptide:**

amino acids 1-17

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**FIGURE 207**

GTTCCGCAGATGCAGAGGTTGAGGTGGCTGCGGGACTGGAAGTCATCGGGCAGAGGTCTC  
ACAGCAGCCAAGGAACCTGGGGCCCGCTCCTCCCCCTCCAGGCCATGAGGATTCTGCAG  
TTAATCCTGCTTGCTCTGGCAACAGGGCTTGTAGGGGGAGAGACCAGGATCATCAAGGGG  
TTCGAGTGCAAGCCTCACTCCCAGCCCTGGCAGGCAGCCCTGTTTCGAGAAGACGCGGCTA  
CTCTGTGGGGCGACGCTCATCGCCCCCAGATGGCTCCTGACAGCAGCCCACTGCCTCAAG  
CCCCGCTACATAGTTCACCTGGGGCAGCACAACTCCAGAAGGAGGAGGGCTGTGAGCAG  
ACCCGGACAGCCACTGAGTCCTTCCCCCACCCTGGCTTCAACAACAGCCTCCCCAACAAA  
GACCACCGCAATGACATCATGCTGGTGAAGATGGCATCGCCAGTCTCCATCACCTGGGCT  
GTGCGACCCCTCACCTCTCCTCACGCTGTGTCACTGCTGGCACCAGCTGCCTCATTTCC  
GGCTGGGGCAGCACGTCCAGCCCCAGTTACGCCTGCCTCACACCTTGCGATGCGCCAAC  
ATCACCATCATTTGAGCACCAGAAGTGTGAGAACGCCTACCCCGGCAACATCACAGACACC  
ATGGTGTGTGCCAGCGTGCAGGAAGGGGGCAAGGACTCCTGCCAGGGTGACTCCGGGGGC  
CCTCTGGTCTGTAACCAGTCTCTTCAAGGCATTATCTCCTGGGGCCAGGATCCGTGTGCG  
ATCACCCGAAAGCCTGGTGTCTACACGAAAGTCTGCAAATATGTGGACTGGATCCAGGAG  
ACGATGAAGAAACAATTAGACTGGACCCACCCACCACAGCCCATCACCTCCATTTCCACT  
TGGTGTTTGGTTCCTGTTCACCTCTGTTAATAAGAAACCCCTAAGCCAAGACCCCTCTACGAA  
CATTCTTTGGGCCTCCTGGACTACAGGAGATGCTGTCACTTAATAATCAACCTGGGGTTC  
GAAATCAGTGAGACCTGGATTCAAATTCTGCCTTGAAATATTGTGACTCTGGGAATGACA  
ACACCTGGTTTGTCTCTGTGTATCCCCAGCCCCAAAGACAGCTCCTGGCCATATATCA  
AGGTTTCAATAAATATTTGCTAAATGAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA  
AAAA

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**FIGURE 208**

MRILQLILLALATGLVGGETRIIKGFECKPHSQPWQAALFEKTRLLCGATLIAPRWLLTA  
AHCLKPRYIVHLGQHNLOKEEGCEQTRTATESFPHPGFNNSLPNKDHRNDIMLVKMASPV  
SITWAVRPLTLSSRCVTAGTSCCLISGWGSTSSPQLRLPHTLRCANITIIIEHQKCENAYPG  
NITDTMVCASVQEGGKDSCQGDSSGGLVCNQSLOGIISWGQDPCAITRKPGVYTKVCKYV  
DWIQETMKNN

**Important features:****Signal peptide:**

amino acids 1-18

**Serine proteases, trypsin family, histidine active site:**

amino acids 58-63

**N-glycosylation sites:**

amino acids 99-102, 165-168, 181-184, 210-213

**Glycosaminoglycan attachment site:**

amino acids 145-148

**Kringle domain proteins:**

amino acids 197-209, 47-64

**Serine proteases, trypsin family, histidine protein:**

amino acids 199-209, 47-63, 220-243

**Apple domain proteins:**

amino acids 222-249, 189-222

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**FIGURE 209**

GCGGCCACACGCAGCTAGCCGGAGCCCGGACCAGGCGCCTGTGCCTCCTCCTCGTCCCTC  
GCCGCGTCCGCGAAGCCTGGAGCCGGCGGGAGCCCCGCGCTCGCCATGTCGGGCGAGCTC  
AGCAACAGGTTCCAAGGAGGGAAGGCGTTTCGGCTTGCTCAAAGCCCGGCAGGAGAGGAGG  
CTGGCCGAGATCAACCGGGAGTTTCTGTGTGACCAGAAGTACAGTGATGAAGAGAACCTT  
CCAGAAAAGCTCACAGCCTTCAAAGAGAAGTACATGGAGTTTGACCTGAACAATGAAGGC  
GAGATTGACCTGATGTCTTTAAAGAGGATGATGGAGAAGCTTGGTGTCCCCAAGACCCAC  
CTGGAGATGAAGAAGATGATCTCAGAGGTGACAGGAGGGGTGAGTACACTATATCCTAC  
CGAGACTTTGTGAACATGATGCTGGGGAAACGGTCGGCTGTCTCAAGTTAGTCATGATG  
TTTGAAGGAAAAGCCAACGAGAGCAGCCCCAAGCCAGTTGGCCCCCTCCAGAGAGAGAC  
ATTGCTAGCCTGCCCTGAGGACCCCGCCTGGACTCCCCAGCCTTCCCACCCCATACCTCC  
CTCCCGATCTTGCTGCCCTTCTTGACACACTGTGATCTCTCTCTCTCATTTGTTTGGT  
CATTGAGGGTTTGTGTTTGTGTTTTCATCAATGTCTTTGTAAAGCACAAATTATCTGCCTTA  
AAGGGGCTCTGGGTCGGGGAATCCTGAGCCTTGGGTCCCCTCCCTCTCTTCTTCCCTCCT  
TCCCCGCTCCCTGTGCAGAAGGGCTGATATCAAACCAAAAAGTAGAGGGGGCAGGGCCAG  
GGCAGGGAGGCTTCCAGCCTGTGTTCCCTCACTTGAGGAACCAGCACTCTCCATCCTT  
TCAGAAAGTCTCCAAGCCAAGTTCAGGCTCACTGACCTGGCTCTGACGAGGACCCAGGC  
CACTCTGAGAAGACCTTGGAGTAGGGACAAGGCTGCAGGGCCTCTTTGGGTTTCTTGG  
ACAGTGCCATGGTTCCAGTGCTCTGGTGTCAACCAGGACACAGCCACTCGGGGCCCCGCT  
GCCCCAGCTGATCCCCACTCATTCACACCTCTTCTCATCCTCAGTGATGTGAAGGTGGG  
AAGGAAAGGAGCTTGGCATTGGGAGCCCTTCAAGAAGGTACCAGAAGGAACCCTCCAGTC  
CTGCTCTCTGGCCACACCTGTGCAGGCAGCTGAGAGGCAGCGTGCAGCCCTACTGTCCCT  
TACTGGGGCAGCAGAGGGCTTCGGAGGCAGAAGTGAGGCCTGGGGTTTGGGGGAAAGGT  
CAGCTCAGTGCTGTTCCACCTTTTAGGGAGGATACTGAGGGGACCAGGATGGGAGAATGA  
GGAGTAAAATGCTCACGGCAAAGTCAGCAGCACTGGTAAGCCAAGACTGAGAAATACAAG  
GTTGCTTGTCTGACCCCAATCTGCTTGAAAAAAAAAAAAAAAAAAAAA

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## FIGURE 210

MSGELSNRFQGGKAFGLLKARQERRLAEGINREFLCDQKYSDEENLPEKLTAFKEKYMED  
LNNEGEIDLMSLKRMMEKLGVPKTHLEMKKMISEVTGGVSDTISYRDFVNMMLGKRSAVL  
KLVMFEGKANESSPKPVGPPPERDIASLP

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**FIGURE 211**

CTGGGATCAGCCACTGCAGCTCCCTGAGCACTCTCTACAGAGACGCGGACCCCAGACATG  
AGGAGGCTCCTCCTGGTCACCAGCCTGGTGGTTGTGCTGCTGTGGGAGGCAGGTGCAGTC  
CCAGCACCCAAGGTCCCTATCAAGATGCAAGTCAAACACTGGCCCTCAGAGCAGGACCCA  
GAGAAGGCCTGGGGCGCCCGTGTGGTGGAGCCTCCGGAGAAGGACGACCAGCTGGTGGTG  
CTGTTCCCTGTCCAGAAGCCGAAACTCTTGACCACCGAGGAGAAGCCACGAGGTGAGGGC  
AGGGGCCCCATCCTTCCAGGCACCAAGGCCTGGATGGAGACCGAGGACACCCTGGGCCGT  
GTCCTGAGTCCCGAGCCCGACCATGACAGCCTGTACCACCCTCCGCCTGAGGAGGACCAG  
GGCGAGGAGAGGCCCCGGTTGTGGGTGATGCCAAATCACCAGGTGCTCCTGGGACCGGAG  
GAAGACCAAGACCACATCTACCACCCCCAGTAGGGCTCCAGGGGCCATCACTGCCCCCGC  
CCTGTCCCAAGGCCCAGGCTGTTGGGACTGGGACCCTCCCTACCCTGCCCCAGCTAGACA  
AATAAACCCCAGCAGGCAAAAAAAAAAAAAAAAAAAAA

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## FIGURE 212

MRRLLLVTSLVVLLWEAGAVPAPKVPIKMQVKHWPSEQDPEKAWGARVVEPPEKDDQLV  
VLFVPVQPKLLTTEEKPRGQGRGPILPGTKAWMETEDTLGRVLSPEPDHDSLYHPPPEED  
QGEERPRLWVMPNHQVLLGPEEDQDHIYHPQ



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**FIGURE 213**

CAGGCAGAAGCGAACAAAGACCCAGCAAGAGAAGGCAGAGGCTAAGACCCATCCCGTATC  
TGCTCTCCTGAAATAATTCTGGAGTCATGCGCTGAAATGCCAGAGGACATGGAGCAGGAGG  
AAGTTAACATCCCTAATAGGAGGGTTCTGGTTACTGGTGCCACTGGGCTTCTTGGCAGAG  
CTGTACACAAAGAATTTACAGCAGAATAATTGGCATGCAGTTGGCTGTGGTTTCAGAAGAG  
CAAGACCAAAAATTTGAACAGGTTAATCTGTTGGATTCTAATGCAGTTCATCACATCATT  
ATGATTTTTCAGCCCCATGTTATAGTACATTGTGCAGCAGAGAGAAGACCAGATGTTGTAG  
AAAATCAGCCAGATGCTGCCTCTCAACTTAATGTGGATGCTTCTGGGAATTTAGCAAAGG  
AAGCAGCTGCTGTTGGAGCATTTCTCATCTACATTAGCTCAGATTATGTATTTGATGGAA  
CAAATCCACCTTACAGAGAGGAAGACATAACCAGCTCCCCTAAATTTGTATGGCAAAACAA  
AATTAGATGGAGAAAAGGCTGTCTGGAGAACAACTAGGAGCTGCTGTTTTGAGGATTC  
CTATTCTGTATGGGGAAGTTGAAAAGCTCGAAGAAAGTGCTGTGACTGTTATGTTTGATA  
AAGTGCAGTTCAGCAACAAGTCAGCAACATGGATCACTGGCAGCAGAGGTTCCCCACAC  
ATGTCAAAGATGTGGCCACTGTGTGCCGGCAGCTAGCAGAGAAGAGAATGCTGGATCCAT  
CAATTAAGGGAACCTTTCACTGGTCTGGCAATGAACAGATGACTAAGTATGAAATGGCAT  
GTGCAATTGCAGATGCCCTTCAACCTCCCCAGCAGTCACTTAAGACCTATTACTGACAGCC  
CTGTCTTAGGAGCACACGTCGAGAAATGCTCAGCTTGACTGCTCCAAATTGGAGACCT  
TGGGCATTGGCCAACGAACACCATTTCAATTGGAATCAAAGAATCACTTTGGCCTTTCC  
TCATTGACAAGAGATGGAGACAAACGGTCTTTCATTAGTTTTATTTGTGTTGGGTTCTTTT  
TTTTTTTTAAATGAAAAGTATAGTATGTGGCACTTTTTTAAAGAACAAAGGAAATAGTTTTG  
TATGAGTACTTTAATTGTGACTCTTAGGATCTTTCAGGTAAATGATGCTCTTGCACTAGT  
GAAATTGTCTAAAGAACTAAAGGGCAGTCATGCCCTGTTTGCAGTAATTTTTCTTTTTTA  
TCATTTTGTGTTGTCCTGGCTAAACTTGGAGTTTGAGTATAGTAAATTATGATCCTTAAAT  
ATTTGAGAGTCAGGATGAAGCAGATCTGCTGTAGACTTTTTCAGATGAAATTGTTTATTCT  
CGTAACCTCCATATTTTCAGGATTTTTGAAGCTGTTGACCTTTTCATGTTGATTATTTTA  
AATTGTGTGAAATAGTATAAAAATCAATTGGTGTTCATTATTTGCTTTGCCTGAGCTCAGA  
TCAAAATGTTTGAAGAAAGGAACCTTTATTTTTGCAAGTTACGTACAGTTTTTATGCTTGA  
GATATTTCAACATGTTATGTATATTGGAACCTTCTACAGCTTGATGCCTCCTGCTTTTATA  
GCAGTTTATGGGGAGCACTTGAAAGAGCGTGTGTACATGTATTTTTTTCTAGGCAAAACA  
TTGAATGCAAACGTGTATTTTTTTAATATAAATATATAACTGTCCTTTTTCATCCCATGTT  
GCCGCTAAGTGATATTTTCATATGTGTGGTTATACTCATAATAATGGGCCTTGTAAGTCTT  
TTCACCATTTCATGAATAATAAATAATATGTACTGCTGGCATGTAATGCTTAGTTTTCTTG  
TATTTACTTCTTTTTTTTAAATGTAAGGACCAAACTTCTAAACTAATTGTTCTTTTGTTGC  
TTTAATTTTTTAAAAATTACATTCTTCTGATGTAACATGTGATACATAAAAAGAATATAG  
TTTAATATGTATTGAAATAAAACACAATAAAATT

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**FIGURE 214**

MPEMPEDMEQEEVNI PNRRVLVTGATGLLGRAVHKEFQQNNWHAVGCGFRRARPKFEQVN  
LLDSNAVHHIIHDFQPHVIVHCAAERRPDVVENQPDAAASQLNVDASGNLAKEAAAVGAFL  
IYISSDYVFDGTNPPYREEDI PAFLNLYGKTKLDGEKAVLENNLGAAVLRIPILYGEVEK  
LEESAVTVMFDKVQFSNKSANMDHWQQRFP THVKDVATVCRQLAEKRMLDPSIKGTFHWS  
GNEQMTKYEMACAIADAFNLPSSHLRPITDSPVLGAQRPRNAQLDCSKLETLGIGQRTPF  
RIGIKESLWPFLIDKRWRQTVFH

**Signal peptide:**  
amino acids 1-30

**Transmembrane domain:**  
amino acids 105-127

**N-glycosylation site:**  
amino acids 197-201

**N-myristoylation site:**  
amino acids 303-309

**Short-chain dehydrogenases/reductases family proteins:**  
amino acids 18-30

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**FIGURE 215**

GTGAATGTGAGGGTTTGATGACTTTTCAGATGTCTAGGAACCAGAGTGGGTGCAGGGGCCC  
CAGGCAGGGCTGATTCTTGGGCGGAGGAGAGTAGGGTAAAGGGTCTGCGATGAGCTCCTT  
AAAGGACAAAGGTAACAGAGCCAGCGAGAGAGCTCGAGGGGAGACTTTGACTTCAAGCCA  
CAGAATTGGTGGAAGTGTGCGCGCCGCCGCCGCTCGCTCCTGCAGCGCTGTGACCTA  
GCCGCTAGCATCTTCCCGAGCACCGGGATCCCGGGGTAGGAGGCGACGCGGGCGAGCACC  
AGCGCCAGCCGGCTGCGGCTGCCCACACGGCTCACCATGGGGCTCCGGGCGCCGGGCGCTG  
TCCGCGGTGCCGGCCGTGCTGCTGGTCTCAGCTGCCGGGGCTGCCCGTCTGGGCACAG  
AACGACACGGAGCCCATCGTGCTGGAGGGCAAGTGTCTGGTGGTGTGCGACTCGAACCCG  
GCCACGGACTCCAAGGGCTCCTCTTCTCCCGCTGGGGATATCGGTCCGGGCGGCCAAC  
TCCAAGGTCGCCTTCTCGGCGGTGCGGAGCACCAACCAGAGCCATCCGAGATGAGCAAC  
AAGACGCGCATCATTTACTTCGATCAGATCCTGGTGAATGTGGGTAATTTTTTTCACATTG  
GAGTCTGTCTTTGTAGCACCAAGAAAAGGAATTTACAGTTTCAGTTTTTCAGTGATTAAA  
GTCTACCAGAGCCAACTATCCAGGTAACTTGATGTTAAATGGAAAACCAGTAATATCT  
GCCTTTGCGGGGGACAAAGATGTTACTCGTGAAGCTGCCACGAATGGTGTCTGCTCTAC  
CTAGATAAAGAGGATAAGGTTTACCTAAACTGGAGAAAGGTAATTTGGTTGGAGGCTGG  
CAGTATTCCACGTTTTCTGGCTTTCTGGTGTTCCTCCCTATAGGATTCAATTTCTCCATGA  
TGTTTCATCCAGGTGAGGGATGACCCACTCCTGAGTTATTGGAAGATCATTTTTTTCATCAT  
TGGATTGATGTCTTTTATTGGTTTCTCATGGGTGGATATGGATTCTAAGGATTCTAGCCT  
GTCTGAACCAATACAAAATTTACAGATTATTTGTGTGTGTCTGTTTTCAGTATATTTGGA  
TTGGGACTCTAAGCAGATAATACCTATGCTTAAATGTAACAGTCAAAAGCTGTCTGCAAG  
ACTTATTCTGAATTTCAATTCCTGGGATTACTGAATTAGTTACAGATGTGGAATTTTATT  
TGTTTAGTTTTTAAAGACTGGCAACCAGGTCTAAGGATTAGAAAACCTCTAAAGTTCTGAC  
TTCAATCAACGGTTAGTGTGATACTGCCAAAGAACTGTATACTGTGTTAATATATTGATT  
ATATTTGTTTTTATTCTTTGGAATTAGTTTGTGTTTGGTTCTTGTAATAAACTTGGATTTT  
TTTTTTTCAGTAACTGGTATTATGTTTTCTCTTAAATAAGGTAATGAATGGCTTGCCAC  
AAATTTACCTTGACTACGATATCATCGACATGACTTCTCTCAAAAAAAAAAGAATGCTTCA  
TAGTTGTATTTTAAATTGTATATGTGAAAGAGTCATATTTTCCAAGTTATATTTTCTAAGA  
AGAAGAATAGATCATAAATCTGACAAGGAAAAAGTTGCTTACCCAAAATCTAAGTGCTCA  
ATCCCTGAGCCTCAGCAAAACAGCTCCCTCCGAGGGAAATCTTATACTTTATTGCTCAA  
CTTTAATTAAATGATTGATAATAACCACTTTATTAAAAACCTAAGGTTTTTTTTTTTTC  
CGTAGACATGACCACTTTATTAAGTGGTGGTGGATGCTGTTGTTTCTAATTATACCTAT  
TTTTCAAGGCTTCTGTTGTATTTGAAGTATCATCTGGTTTTCCTTAACTCTTTAAATTG  
TATATATTTATCTGTTTAGCTAATATTAATTTCAAATATCCCATATCTAAATTTAGTGCA  
ATATCTTGCTTTTGTATAGGTCATATGAATTCATAAAATTATTTATGTCTGTTATAGAA  
TAAAGATTAAATATATGTTAAAAAAA

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**FIGURE 216**

MSGRRALSAVPAVLLVLTLPGLPVWAQNDTEPIVLEGKCLVVCDSPATDSKGSSSSPL  
GISVRAANSKVAFS AVRSTNHEPSEMSNKTRIIYFDQILVNVGNFFTLESV FVAPRKGIY  
SFSFHVIVKYQSQTIQVNLMLNGKPVISAFAGDKDVTREATNGVLLYLDKEDKVYLKLE  
KGNLVGGWQYSTFSGFLVFPL

**Signal peptide:**  
amino acids 1-27

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**FIGURE 217**

CGGCAACCAGCCGCGCCACCACCGCTGCCACTGCCGCCCTGCCGGGGCCATGTTTCGCTC  
TGGGCTTGCCCTTCTTGGTGCTCTTGGTGGCCTCGGTGAGAGCCATCTGGGGGTTCTGG  
GGCCCAAGAACGTCTCGCAGAAAGACGCCGAGTTTGAGCGCACCTACGTGGACGAGGTCA  
ACAGCGAGCTGGTCAACATCTACACCTTCAACCATACTGTGACCCGCAACAGGACAGAGG  
GCGTGCGTGTGTCTGTGAACGTCTGAACAAGCAGAAGGGGGCGCCGTTGCTGTTTGTGG  
TCCGCCAGAAGGAGGCTGTGGTGTCTTCCAGGTGCCCCCTAATCCTGCGAGGGATGTTTC  
AGCGCAAGTACCTCTACCAAAAAGTGGAACGAACCCTGTGTGAGCCCCCACCAGAATG  
AGTCGGAGATTGAGTTCTTCTACGTGGATGTGTCCACCCTGTGACCAAGTCAACACCACAT  
ACCAGCTCCGGGTGAGCCGCATGGACGATTTTGTGCTCAGGACTGGGGAGCAGTTGAGCT  
TCAATACCACAGCAGCACAGCCCCAGTACTTCAAGTATGAGTTCCCTGAAGGCGTGGACT  
CGGTAATTGTCAAGGTGACCTCCAACAAGGCCTTCCCCTGCTCAGTCATCTCCATTGAGG  
ATGTGCTGTGTCTGTCTATGACCTGGACAACAACGTAGCCTTCATCGGCATGTACCAGA  
CGATGACCAAGAAGGCGGCCATCACCCTACAGCGCAAAGACTTCCCCAGCAACAGCTTTT  
ATGTGGTGGTGGTGGTGAAGACCGAAGACCAAGCCTGCCGGGGCTCCCTGCCCTTCTACC  
CCTTCGCAGAAGATGAACCGGTGATCAAGGGCACCGCCAGAAAACCCTGTGAGTGTGG  
TGTCTCAAGCAGTCACGTCTGAGGCATACGTGAGTGGGATGCTCTTTTGCCTGGGTATAT  
TTCTCTCCTTTTACCTGCTGACCGTCCTCCTGGCCTGCTGGGAGAACTGGAGGCAGAAGA  
AGAAGACCCTGCTGGTGGCCATTGACCGAGCCTGCCAGAAAAGCGGTACCCCTCGAGTCC  
TGGCTGATTCTTTTCTGGCAGTTCCCCTTATGAGGGTTACAACTATGGCTCCTTTGAGA  
ATGTTTCTGGATCTACCGATGGTCTGGTTGACAGCGCTGGCACTGGGGACCTCTCTTACG  
GTTACCAGGGCCGCTCCTTTGAACCTGTAGGTACTCGGCCCCGAGTGGACTCCATGAGCT  
CTGTGGAGGAGGATGACTACGACACATTGACCGACATCGATTCCGACAAGAATGTGATTC  
GCACCAAGCAATACCTCTATGTGGCTGACCTGGCACGGAAGGACAAGCGTGTCTGCGGA  
AAAAGTACCAGATCTACTTCTGGAACATTGCCACCATTGCTGTCTTCTATGCCCTTCTTG  
TGGTGCAGCTGGTGATCACCTACCAGACGGTGGTGAATGTACAGGGAATCAGGACATCT  
GCTACTACAACTTCTCTGCGCCCACCCACTGGGCAATCTCAGCGCCTTCAACAACATCC  
TCAGCAACCTGGGGTACATCCTGCTGGGGCTGCTTTTCTGCTCATCATCTGCAACGGG  
AGATCAACCACAACCGGGCCCTGCTGCGCAATGACCTCTGTGCCCTGGAATGTGGGATCC  
CCAAACACTTTGGGCTTTTCTACGCCATGGGCACAGCCCTGATGATGGAGGGGCTGCTCA  
GTGCTTGCTATCATGTGTGCCCCAACTATACCAATTTCCAGTTTGACACATCGTTGATGT  
ACATGATCGCCGACTCTGCATGCTGAAGCTCTACCAGAAGCGGCACCCGGACATCAACG  
CCAGCGCTACAGTGCTACGCCTGCCTGGCCATTGTGATCTTCTTCTCTGTGCTGGGCG  
TGGTCTTTGGCAAAGGGAACACGGCGTTCTGGATCGTCTTCTCCATCATTACATCATCG  
CCACCCTGCTCCTCAGCACGCAGCTCTATTACATGGGCGGTGGAACTGGACTCGGGGA  
TCTTCCGCCGCATCCTCCACGTGCTCTACACAGACTGCATCCGGCAGTGCAGCGGGCCGC  
TCTACGTGGACCGCATGGTGTGCTGCTGGTATGGGCAACGTGATCAACTGGTGGCTGGCTG  
CCTATGGGCTTATCATGCGCCCCAATGATTTGCTTCTTCTACTTGTGGCCATTGGCATCT  
GCAACCTGCTCCTTTACTTGCCTTCTACATCATCATGAAGCTCCGGAGTGGGGAGAGGA  
TCAAGCTCATCCCCCTGCTCTGCATCGTTTGACCTCCGTGGTCTGGGGCTTCGCGCTCT  
TCTTCTTCTTCCAGGGACTCAGCACCTGGCAGAAAACCCCTGCAGAGTCGAGGGAGCACA  
ACCGGGACTGCATCCTCCTCGACTTCTTTGACGACCACGACATCTGGCACTTCTCTCTCT  
CCATCGCCATGTTGCGGTCTTCTGGTGTGCTGACACTGGATGACGACCTGGATACTG  
TGCAGCGGGACAAGATCTATGTCTTCTAGCAGGAGCTGGGCCCCCTCGCTTCACTCAAGG  
GGCCCTGAGCTCCTTTGTGTGATAGACCGGTCACTCTGTGCTGTGTTGGGGATGAGTCCC  
AGCACCGCTGCCAGCACTGGATGGCAGCAGGACAGCCAGGTCTAGCTTAGGCTTGGCCT  
GGGACAGCCATGGGGTGGCATGGAACCTTGACGCTGCCCTCTGCCGAGGAGCAGGCCTGC  
TCCCCTGGAACCCCCAGATGTTGGCCAAATTGCTGCTTTCTTCTCAGTGTGGGGCCTTC

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CATGGGGCCCCTGTCCCTTTGGCTCTCCATTTGTCCCTTTGCAAGAGGAAGGATGGAAGGGA  
CACCCCTCCCCATTTTCATGCCTTGCATTTTGGCCGTCTCCTCCCCACAATGCCCCAGCCT  
GGGACCTAAGGCCTCTTTTCCCTCCCATACTCCCACTCCAGGGCCTAGTCTGGGGCCTGA  
ATCTCTGTCTGTATCAGGGCCCCAGTTCTCTTTGGGCTGTCCCTGGCTGCCATCACTGC  
CCATTCCAGTCAGCCAGGATGGATGGGGGTATGAGATTTTGGGGGTGGCCAGCTGGTGC  
CAGACTTTTGGTGCTAAGGCCTGCAAGGGGCCTGGGGCAGTGCGTATTCTCTTCCCTCTG  
ACCTGTGCTCAGGGCTGGCTCTTTAGCAATGCGCTCAGCCCAATTTGAGAACCGCCTTCT  
GATTCAAGAGGCTGAATTCAGAGGTCACCTCTTCATCCCATCAGCTCCCAGACTGATGCC  
AGCACCAGGACTGGAGGGAGAAGCGCCTCACCCCTTCCCTTCTTCCAGGCCCTTA  
GTCTTGCCAAACCCCAGCTGGTGGCCTTTTCAGTGCCATTGACACTGCCCAAGAATGTCCA  
GGGGCAAAGGAGGGATGATACAGAGTTTCAGCCCGTTCTGCCTCCACAGCTGTGGGCACCC  
CAGTGCCCTACCTTAGAAAAGGGGCTTCAGGAAGGGATGTGCTGTTTCCCTCTACGTGCCCA  
GTCCTAGCCTCGCTCTAGGACCCAGGGCTGGCTTCTAAGTTTCCGTCCAGTCTTCAGGCA  
AGTTCTGTGTTAGTCATGCACACACATACCTATGAAACCTTGGAGTTTACAAAGAATTGC  
CCCAGCTCTGGGCACCCCTGGCCACCCTGGTCCTTGGATCCCCTTCGTCCCACCTGGTCCA  
CCCCAGATGCTGAGGATGGGGGAGCTCAGGCGGGGCCTCTGCTTTGGGGATGGGAATGTG  
TTTTTCTCCCAAACCTTGTTTTATAGCTCTGCTTGAAGGGCTGGGAGATGAGGTGGGTCT  
GGATCTTTTCTCAGAGCGTCTCCATGCTATGGTTGCATTTCCGTTTTCTATGAATGAATT  
TGCATTCAATAAACCAACCAGACTCAAAAAAAAAAAAAAA

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**FIGURE 218**

MFALGLPFLVLLVASVESHGVLGPKNVSQKDAEFERTYVDEVNSELVNIYTFNHTVTRN  
RTEGVRVSVNVLNKQKGAPLLFVVRQKEAVVSFQVPLILRGMFQRKYLYQKVERTLCQPP  
TKNESEIQFFYVDVSTLSPVNTTYQLRVSRMDDFVLRRTGEQFSFNTTAAQPQYFKYEFPE  
GVDSVIVKVTSNKAFFPCSVISIQDVLCVPYDLNNAFIGMYQTMTKKAAITVQRKDFPS  
NSFYVVVVVKTEDQACGGSLPFYPFAEDEPVDQGHRQKTL SVLVSQAVTSEAYVSGMLFC  
LGIFLSFYLLTVLLACWENWRQKKKTLLVAIDRACPESGHPRVLADSFPGSSPYEGYNYG  
SFENVSGSTDGLVDSAGTGDLSEYGYQGRSFEPVGTRPRVDSMSSVEEDDYDTLTDIDSDK  
NVIRTKQYLYVADLARKDKRVLRRKKYQIYFWNIATIAVFYALPVVQLVITYQTVVNVNVTGN  
QDICYNNFLCAHPLGNLSAFNNILSNLGYILLGLLFLLIILQREINHNRRALLRNDLCALE  
CGIPKHFGLFYAMGTALMMEGLLSACYHVCNPNYTNFQFDTSEFMYMIAGLCMLKLYQKRHP  
DINASAYSAYACLAIVIFFSVLGVVFGKGNATFWIVFSIIHIIATLLLSTQLYYMGRWKL  
DSGIFRRILHVLYTDCIRQCSGPLYVDRMVLLVMGNVINWSLAAYGLIMRPNDFASYLLA  
IGICNLLLYFAFYIIMKLRSGERIKLIPLLCIVCTSVVWGFALFFFFQGLSTWQKTPAES  
REHNRDCILLDFDDHDIWHFLSSIAMFGSFLVLLTLDDDLDTVQRDKIYVF

**Important features of the protein:****Signal peptide:**

amino acids 1-18

**Transmembrane domains:**

amino acids 292-317, 451-470, 501-520, 607-627, 751-770

**Leucine zipper pattern:**

amino acids 497-518

**N-glycosylation sites:**amino acids 27-30, 54-57, 60-63, 123-126, 141-144, 165-168,  
364-367, 476-479, 496-499, 572-575, 603-606, 699-702





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**FIGURE 220**

MRSTILLFCLLGSTRSLPQLKPALGLPPTKLAPDQGTLPNQQQSNQVFPSSLISLIPLTQML  
TLGPDHLHLNPAAGMTPGTQTHPLTLGGLNVQQQLHPHVLPIFVTQLGAQGTLISSEELP  
QIFTSLIIHSLFPGGILPTSQAGANPDVQDGSLLPAGGAGVNPATQGTPAGRLPTPSGTDD  
DFAVTPPAGIQRSTHAIEEATTESANGIQ

**Signal peptide:**  
amino acids 1-16



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**FIGURE 222**

MARMSFVIAACQLVLGGLMTSLTESSIONSECPQLCVCEIRPWFTPOSTYREATTVDCND  
LRLTRIPSNLSSDTQVLLQLQSNNIKTVDLQQLFNLTELDIFSQNNFTNIKEVGLANLTQ  
LTTLHLEENQITEMTDYCLQDLNLQELYINHNOISTISAHAFAGLKNLLRLHLNSNKLK  
VIDSRWFDSTPNLEILMIGENPVIGILDMNFKPLANLRSLVLAGMYLTDIPGNALVGLDS  
LESLSFYDNKLVKVPQLALQKVPNLKFLDLNKNPIHKIQEGDFKNMLRLKELGINNMGEL  
VSVDRYALDNLPELTKLEATNNPKLSYIHLAFRSVPALSLMLNNNALNAIYQKTVESL  
PNLREISIHNSNPLRCDLVIHWINSNKTNIREFMEPLSMFCAMPPEYKGHVKEVLIQDSSE  
QCLPMISHDSFPNRLNVDIGTTVFLDCRAMAEPEPEIYWVTPIGNKITVETLSDKYKLSS  
EGTLEISNIQIEDSGRYTCVAQNVQGADTRVATIKVNGTLLDGTQVLKIYVKQTESHSL  
VSWKVNSNVMTSNLKWSSATMKIDNPHITYTARVPVDVHEYNLTHLQPDYEVCLTVSN  
IHQQTQKSCVNVTTKNAAFVADISDQETSTALAAVMGSMFAVISLASIAVYFAKRFRKN  
YHHSCLKKYMOKTSSIPNLNELYPPPLINLWEGDSEKDKDGSADTKPTQVDTSRSSYYMW

**Important features:****Signal peptide:**

Amino acids 1-25

**Transmembrane domain:**

Amino acids 508-530

**N-glycosylation sites:**Amino acids 69-73;96-100;106-110;117-121;385-389;517-521;  
582-586;611-615**Tyrosine kinase phosphorylation site:**

Amino acids 573-582

**N-myristoylation sites:**

Amino acids 16-22;224-230;464-470;637-643;698-704

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**FIGURE 223**

[illegible]

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**FIGURE 224**

MASYLYGVLFVAVGLCAPIYCVSPANAPSAYPRPSSTKSTPASQVYSLNTDFAFRLYRRLV  
LETPSQNIFFSPVSVSTSLAMLSLGAHSVTKTQILQGLGFNLTHTPESAIHQGFQHLVHS  
LTVPSKDLTLKMGSALFVKKELQLQANFLGNVKRLYEAEVFSTDFSNPSIAQARINSHVK  
KKTQGKVVDIIQGLDLLTAMVLVNHIFFKAKWEKPFHLEYTRKNFPFLVGEQVTVQVPMM  
HQKEQFAFGVDTELNCFVLQMDYKGDVAFFVLPSKGKMRQLEQALSARTLIKWSHSLQK  
RWIEVFIPRFSISASYNLETILPKMGIQNAFDKNADFSGIAKRDSLQVSKATHKAVLDVS  
EEGTEATAATTTKFIVRSKDGPSYFTVSFNRTFLMMITNKATDGILFLGKVENPTKS

**Signal peptide:**  
amino acids 1-20

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**FIGURE 225**

GGGAGAGAGGATAAATAGCAGCGTGGCTTCCCTGGCTCCTCTCTGCATCCTTCCCGACCT  
TCCCAGCAATATGCATCTTGACGTCTGGTCGGCTCCTGCTCCCTCCTTCTGCTACTGGG  
GGCCCTGTCTGGATGGGCGGCCAGCGATGACCCATTGAGAAGGTCATTGAAGGGATCAA  
CCGAGGGCTGAGCAATGCAGAGAGAGAGGTGGGCAAGGCCCTGGATGGCATCAACAGTGG  
AATCACGCATGCCGGAAGGGAAGTGGAGAAGGTTTTCAACGGACTTAGCAACATGGGGAG  
CCACACCGGCAAGGAGTTGGACAAAGGCGTCCAGGGGGCTCAACCACGGCATGGACAAGGT  
TGCCCATGAGATCAACCATGGTATTGGACAAGCAGGAAAGGAAGCAGAGAAGCTTGGCCA  
TGGGGTCAACAACGCTGCTGGACAGGCCGGGAAGGAAGCAGACAAAGCGGTCCAAGGGTT  
CCACACTGGGGTCCACCAGGCTGGGAAGGAAGCAGAGAACTTGGCCAAGGGGTCAACCA  
TGCTGCTGACCAGGCTGGAAAGGAAGTGGAGAAGCTTGGCCAAGGTGCCACCATGCTGC  
TGGCCAGGCCGGGAAGGAGCTGCAGAATGCTCATAATGGGGTCAACCAAGCCAGCAAGGA  
GGCCAACCAGCTGCTGAATGGCAACCATCAAAGCGGATCTTCCAGCCATCAAGGAGGGGC  
CACAACCACGCCGTTAGCCTCTGGGGCCTCAGTCAACACGCCTTTCATCAACCTTCCCGC  
CCTGTGGAGGAGCGTCGCCAACATCATGCCCTTAAACTGGCATCCGGCCTTGCTGGGAGAA  
TAATGTCGCCGTTGTACATCAGCTGACATGACCTGGAGGGGTGGGGGTGGGGGACAGG  
TTTCTGAAATCCCTGAAGGGGGTTGTACTGGGATTTGTGAATAAACTTGATACACCA

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**FIGURE 226**

MHLARLVGSCSLLLLLLGALSGWAASDDPIEKVIEGINRGLSNAEREVGKALDGINSGITH  
AGREVEKVFNGLSNMGSHGTGKELDKGVQGLNHGMDKVAHEINHGIGQAGKEAEKLGHGVN  
NAAGQAGKEADKAVQGFHTGVHQAGKEAEKLGQGVNHAADQAGKEVEKLGQGAHHAAGQA  
GKELQNAHNGVNVQASKEANQLLNGNHQSGSSSHQGGATTTPLASGASVNTPFINLPALWR  
SVANIMP

**Important features of the protein:**

**Signal peptide:**

amino acids 1-25

**Homologous region to circumsporozoite (CS) repeats:**

amino acids 35-225

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**FIGURE 227**

GAAGTAGAGGTGTTGTGCTGAGCGGCGCTCGGCGAACTGTGTGGACCGTCTGCTGGGACT  
CCGGCCCTGCGTCCGCTCAGCCCCGTGGCCCCGCGCACCTACTGCCATGGGAGACGCGGCC  
TCGTCTCGGGGCCACCTGTTTGCTGGGCTTCAGTTTCCTGCTCCTCGTCATCTCTTCTGA  
TGGACATAATGGGCTTGGAAGGGTTTTGGAGATCATATTCATTGGAGGACACTGGAAGA  
TGGGAAGAAAGAAGCAGCTGCCAGTGGACTGCCCCTGATGGTGATTATTCATAAATCCTG  
GTGTGGAGCTTGCAAAGCTCTAAAGCCCAAATTTGCAGAATCTACGGAAATTCAGAACT  
CTCCCATAAATTTTGTTATGGTAAATCTTGAGGATGAAGAGGAACCCAAAGATGAAGATTT  
CAGCCCTGACGGGGGTTATATTCACGAATCCTTTTTCTGGATCCCAGTGGCAAGGTGCA  
TCCTGAAATCATCAATGAGAATGGAAACCCAGCTACAAGTATTTTATGTCAGTGCCGA  
GCAAGTTGTTCAGGGGATGAAGGAAGCTCAGGAAAGGCTGACGGGTGATGCCTTCAGAAA  
GAAACATCTTGAAGATGAATTGTAACATGAATGTGCCCTTCTTTCATCAGAGTTAGTGT  
TCTGGAAGGAAAGCAGCAGGGAAGGGAATATTGAGGAATCATCTAGAACAATTAAGCCGA  
CCAGGAAACCTCATTCCTACCTACACTGGAAGGAGCGCTCTCACTGTGGAAGAGTTCTGC  
TAACAGAAGCTGGTCTGCATGTTTGTGGATCCAGCGGAGAGTGGCAGACTTCTTCTCCT  
TTTCCCTCTCACCTAAATGTCAACTTGTGTCATTGAATGTAAAGAATGAAACCTTCTGACAC  
AAAA



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## FIGURE 228

METRPRLGATCLLGFSFLLLVISSDGHNGLGKGFGDHIHWRTLEDGKKEAAASGLPLMVI  
IHKSWCGACKALKPKFAESTEISELSHNFVMVNLEDEEPEKDEDFSPDGGYIPRILFLDP  
SGKVHPEIINENGNP SYKYFYVSAEQVVG MKEAQERLTGDAFRKKHLEDEL

**Signal peptide:**  
Amino acids 1-23

**Thioredoxin family proteins Homology Block:**  
Amino acids 58-75

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**FIGURE 229**

CCCACGCGTCCGCCCACGCGTCCGGGTGCCACTCGCGCGCCGGCCGCGCTCCGGGCTTCT  
CTTTTCCCTCCGACGCGCCACGGCTGCCCAGACATTCCGGCTGCCGGGTCTGGAGAGCTC  
CCCGAACCCCTCCGCGGAGAGGAGCGAGGCGGCGCCAGGGTGGCCCCCGGGGCGCGCTTG  
GTCTCGGAGAAGCGGGGACGAGGCCGAGGATGAGCGACTGAGGGCGACGCGGGCACTGA  
CGCGAGTTGGGGCCGCGACTACCGGCAGCTGACAGCGCGATGAGCGACTCCCCAGAGACG  
CCCTAGCCCCGGTGTGCGCGCCAGGCGGAGCGCGCAGGTGGGGCTGGGCTGTTAGTGGTCC  
GCCCCACGCGGGTGC CGCGCCGCGCCAGGATGGGCGCTGGCAACCCGGGCCCCGCGCCCGC  
CGCTGCTACCCCTGCGCCCGCTGCGAGCCCGGCGTCCGGCCCCGCGCCCTGCGCTCATGGA  
CGGCGGCTCCCGGCTGGCGGCGGCGCGCCCCCGGGCTGTGAATGCGACTCGCCCCCTCGGC  
CGCGCTCCCCGCCCCGCCCCGCCCCGCGGGACGTGGTAGGGGATGCCAGCTCCACTGCGAT  
GGCAGTTGGCGCGCTCTCCAGTTCCCTCCTGGTCACTGCTGCCTGATGGTGGCTCTGTG  
CAGTCCGAGCATCCCGCTGGAGAAGCTGGCCAGGCACCAGAGCAGCCGGGCCAGGAGAA  
GCGTGAGCACGCCACTCGGGACGGCCCCGGGGCGGGTGAACGAGCTCGGGCGCCCCGGCGAG  
GGACGAGGGCGGCAGCGGCCGGGACTGGAAGAGCAAGAGCGGCCGTGGGCTCGCCGGCCG  
TGAGCCGTGGAGCAAGCTGAAGCAGGCCTGGGTCTCCAGGGCGGGGGCGCCAAGGCCGG  
GGATCTGCAGGTCCGGCCCCGCGGGGACACCCCGCAGGCGGAAGCCCTGGCCGCAGCCGC  
CCAGGACGCGATTGGCCCCGAACTCGCGCCCACGCCCCGAGCCACCCGAGGAGTACGTGTA  
CCCGGACTACCGTGGCAAGGGCTGCGTGGACGAGAGCGGCTTCGTGTACGCGATCGGGGA  
GAAGTTCGCGCCGGGCCCCCTCGGCCTGCCCGTGCCTGTGCACCGAGGAGGGGCCGCTGTG  
CGCGCAGCCCCAGTGCCCGAGGCTGCACCCGCGCTGCATCCACGTGACACGAGCCAGTG  
CTGCCCGCAGTGCAAGGAGAGGAAGAACTACTGCGAGTTCGGGGCAAGACCTATCAGAC  
TTTGAGGAGTTCTGTTGTCTCCATGCGAGAGGTGTGCTGTGAAGCCAACGGTGAGGT  
GCTATGCACAGTGTGAGCGTGTCCCCAGACGGAGTGTGTGGACCCTGTGTACGAGCCTGA  
TCAGTGCTGTCCCATCTGCAAAAATGGTCCAAACTGCTTTGCAGAAACCGCGGTGATCCC  
TGCTGGCAGAGAAGTGAAGACTGACGAGTGCACCATATGCCACTGTACTTATGAGGAAGG  
CACATGGAGAATCGAGCGGCAGGCCATGTGCACGAGACATGAATGCAGGCAAATGTAGAC  
GTTTCCCAGAACACAAACTCTGACTTTTTTCTAGAACATTTTACTGATGTGAACATTCTAG  
ATGACTCTGGGAACATCAGTCAAAGAAGACTTTTGGATGAGGAATAATGGAAAATTGTTG  
GTACTTTTCTTTTCTTGATAACAGTTACTACAACAGAAGGAAATGGATATATTTTCAAAA  
CATCAACAAGAACTTTGGGCATAAAATCCTTCTCTAAATAAATGTGCTATTTTCACAGTA  
AGTACACAAAAGTACACTATTATATATCAAATGTATTTCTATAATCCCTCCATTAGAGAG  
CTTATATAAGTGTTTTCTATAGATGCAGATTAAAAATGCTGTGTTGTCAACCGTCAAAAA  
AAAAAAAAAAAAAAAAAAAAA

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**FIGURE 230**

MPSSTAMAVGALSSSLVTCCLMVALCSPSIPLEKLAQAPEQPGQEKREHATRDGPGRVN  
ELGRPARDEGGSGRDWKS KSGRGLAGREPWSKLKQAWVSQGGGAKAGDLQVRPRGDTPOA  
EALAAAAQDAIGPELAPTPEPPEEYVYPDYRGKGCVDSESGFVYAIGKFPAGGPSACPCLC  
TEEGPLCAQPECPRLHPRCIHVDTSQCCPQCKERKNYCEFRGKTYQTLEEFVVSPECRCR  
CEANGEVLCTVSACPQTECVDPVYEPDQCCPICKNGPNCFAETA VIPAGREVKTDECTIC  
HCTYEETWRIERQAMCTRHECRQM

**Important features of the protein:**

**Signal peptide:**

amino acids 1-27

**Transmembrane domain:**

amino acids 11-30

**Glycosaminoglycan attachment site:**

amino acids 80-83

**N-myristoylation sites:**

amino acids 10-15, 102-107, 103-108

**Cell attachment sequence:**

amino acids 114-117

**EGF-like domain cysteine pattern signature:**

amino acids 176-187

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**FIGURE 231**

GGCCGGACGCCTCCGCGTTACGGGATGAATTAACGGCGGGTTCCGCACGGAGGTTGTGAC  
CCCTACGGAGCCCCAGCTTGCCACGCACCCCACTCGGCGTCGCGCGGCGTGCCCTGCTT  
GTCACAGGTGGGAGGCTGGAACATATCAGGCTGAAAAACAGAGTGGGTACTCTCTTCTGGG  
AAGCTGGCAACAAATGGATGATGTGATATATGCATTCCAGGGGAAGGGAAATTGTGGTGC  
TTCTGAACCCATGGTCAATTAACGAGGCAGTTTCTAGCTACTGCACGTACTTCATAAAGC  
AGGACTCTAAAAGCTTTTGGGAATCATGGTGTATGGAAAGGGATTACTTTTATACTGACTC  
TGTTTTGGGGAAGCTTTTTTGGGAAGCATTTTCATGCTGAGTCCCTTTTTACCTTTGATGT  
TTGTAAACCCATCTTGGTATCGCTGGATCAACAACCGCCTTGTGGCAACATGGCTCACCC  
TACCTGTGGCATTATTGGAGACCATGTTTGGTGTAAAAGTGATTATAACTGGGGATGCAT  
TTGTTCTTGGAGAAAGAAGTGTCATTATCATGAACCATCGGACAAGAATGGACTGGATGT  
TCCTGTGGAATTGCCTGATGCGATATAGCTACCTCAGATTGGAGAAAATTTGCCTCAAAG  
CGAGTCTCAAAGGTGTTCTTGGATTGTGGTGGGCCATGCAGGCTGCTGCCTATATCTTCA  
TTCATAGGAAATGGAAGGATGACAAGAGCCATTTTGAAGACATGATTGATTACTTTTGTG  
ATATTCACGAACCACTTCAACTCCTCATATTTCCAGAAGGGACTGATCTCACAGAAAACA  
GCAAGTCTCGAAGTAATGCATTTGCTGAAAAAATGGACTTCAGAAATATGAATATGTTT  
TACATCCAAGAACTACAGGCTTTACTTTTGTGGTAGACCGTCTAAGAGAAGGTAAGAACC  
TTGATGCTGTCCATGATATCACTGTGGCGTATCCTCACAAACATTCTCAATCAGAGAAGC  
ACCTCCTCCAAGGAGACTTTCCAGGGAAATCCACTTTACGTCCACCGGTATCCAATAG  
ACACCTTCCCCACATCCAAGGAGGACCTTCAACTCTGGTGCCACAAACGGTGGGAAGAGA  
AAGAAGAGAGGCTGCGTTCCTTCTATCAAGGGGAGAAGAATTTTTATTTTACCGGACAGA  
GTGTCAATCCACCTTGCAAGTCTGAACTCAGGGTCCTTGTGGTCAAATTGCTCTCTATAC  
TGTATTGGACCCTGTTTCAAGCCCTGCAATGTGCCTACTCATATATTTGTACAGTCTTGTTA  
AGTGGTATTTTATAATCACCATTGTAATCTTTGTGCTGCAAGAGAGAATATTTGGTGGAC  
TGGAGATCATAGAACTTGATGTTACCGACTTTTACACAAACAGCCACATTTAAATTCAA  
AGAAAAATGAGTAAAGATTATAAGGTTTGCCATGTGAAAACCTAGAGCATATTTTGGAAT  
GTTCTAAACCTTTCTAAGCTCAGATGCATTTTTCATGACTATGTGCAATATTTCTTACT  
GCCATCATTATTTGTTAAAGATATTTTGCACCTAATTTTGTGGGAAAAATATTGCTACAA  
TTTTTTTTTAATCTCTGAATGTAATTTTCGATACTGTGTACATAGCAGGGAGTGATCGGGGT  
GAAATAACTTGGGCCAGAATATTATTAAACAATCATCAGGCTTTTAAA

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**FIGURE 232**

MHSRGREIVVLLNPWSINEAVSSYCTYFIKQDSKSFSGIMVSWKGIYFILTLFWGSFFGSI  
FMLSPFLPLMFVNPSWYRWINNRLVATWLTLPVALLETMFGVKVIITGDAFVPGERSVII  
MNHRTMDWMFLWNCLMRYSYLRLEKICLKASLKGVPFGFWAMQAAAYIFIHRKWDDKS  
HFEDMIDYFCDIHEPLQLLIFPEGTDLTENSKSRSNAFAEKNGLQKYEYVLHPRTTGFTF  
VVDRLREGKNLDAVHDITVAYPHNIPQSEKHLQGDFFPREIHFHVHRYPIDTLPTSKEDL  
QLWCHKRWEEKERLRSFYQGEKNFYFTGQSVIPPCKSELRLVVKLLSILYWTFLFSPAM  
CLLIYLYSLVKWYFIITIVIFVLQERIFGGLEIIEIACRYRLHKKQPHLNSKKNE

**Important features of the protein:**

**Signal peptide:**

amino acids 1-22

**Transmembrane domains:**

amino acids 44-63, 90-108, 354-377

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**FIGURE 233**

CGGCTCGAGTGCAGCTGTGGGGAGATTTTCAGTGCATTGCCTCCCCTGGGTGCTCTTCATC  
TTGGATTTGAAAGTTGAGAGCAGCATGTTTTGCCCCACTGAAACTCATCCTGCTGCCAGTG  
TACTGGATTATTCCTTGGGCCTGAATGACTTGAATGTTTCCCCGCTGAGCTAACAGTC  
CATGTGGGTGATTTCAGCTCTGATGGGATGTGTTTTCCAGAGCACAGAAGACAAATGTATA  
TTCAAGATAGACTGGACTCTGTCACCAGGAGAGCACGCCAAGGACGAATATGTGCTATAC  
TATTACTCCAATCTCAGTGTGCCTATTGGGCGCTTCCAGAACCGCGTACACTTGATGGGG  
GACATCTTATGCAATGATGGCTCTCTCCTGCTCCAAGATGTGCAAGAGGCTGACCAGGGA  
ACCTATATCTGTGAAATCCGCCTCAAAGGGGAGAGCCAGGTGTTCAAGAAGGCGGTGGTA  
CTGCATGTGCTTCCAGAGGAGCCCAAAGAGCTCATGGTCCATGTGGGTGGATTGATTCAG  
ATGGGATGTGTTTTCCAGAGCACAGAAGTGAAACACGTGACCAAGGTAGAATGGATATTT  
TCAGGACGGCGCGCAAAGGAGGAGATTGTATTTCTGTTACTACCACAACTCAGGATGTCT  
GTGGAGTACTCCAGAGCTGGGGCCACTTCCAGAATCGTGTGAACCTGGTGGGGGACATT  
TTCCGCAATGACGGTTCATCATGCTTCAAGGAGTGAGGGAGTCAGATGGAGGAAACTAC  
ACCTGCAGTATCCACCTAGGGAACCTGGTGTTCAGAAAACCATTGTGCTGCATGTCAGC  
CCGGAAGAGCCTCGAACACTGGTGACCCCGGCAGCCCTGAGGCCTCTGGTCTTGGGTGGT  
AATCAGTTGGTGATCATTGTGGGAATTGTCTGTGCCACAATCCTGCTGCTCCCTGTTCTG  
ATATTGATCGTGAAGAAGACCTGTGGAAATAAGAGTTCAGTGAATTCTACAGTCTTGGTG  
AAGAACACGAAGAAGACTAATCCAGAGATAAAAGAAAAACCCTGCCATTTTGAAAGATGT  
GAAGGGGAGAAACACATTTACTCCCCAATAATTGTACGGGAGGTGATCGAGGAAGAAGAA  
CCAAGTGAAAAATCAGAGGCCACCTACATGACCATGCACCCAGTTTGGCCTTCTCTGAGG  
TCAGATCGGAACAACTCACTTGAAAAAAGTCAGGTGGGGGAATGCCAAAAACACAGCAA  
GCCTTTTGAGAAGAATGGAGAGTCCCTTCATCTCAGCAGCGGTGGAGACTCTCTCCTGTG  
TGTGTCCTGGGCCACTCTACCAGTGATTTTCAGACTCCCGCTCTCCAGCTGTCTCCTGT  
CTCATTGTTTGGTCAATACACTGAAGATGGAGAATTTGGAGCCTGGCAGAGAGACTGGAC  
AGCTCTGGAGGAACAGGCCTGCTGAGGGGAGGGGAGCATGGACTTGGCCTCTGGAGTGGG  
ACACTGGCCCTGGGAACCAGGCTGAGCTGAGTGGCCTCAAACCCCCCGTTGGATCAGACC  
CTCCTGTGGGCAGGGTTCTTAGTGGATGAGTTACTGGGAAGAATCAGAGATAAAACCAA  
CCCAAATCAA

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**FIGURE 234**

MFCPLKLILLPVLLDYSLGLNDLNVSPPELTVHVGDSALMGCVFQSTEDKCIFKIDWTLS  
PGEHAKDEYVLYYYSNLSVPIGRFQNRVHLMGDILCNDGSLLLQDVQEADQGTIICEIRL  
KGESQVFKKAVVLHVLPEEPKELMVHVGGLIQMGCVFQSTEVKHVTKVEWIFSGRRAKEE  
IVFRYYHKL RMSVEYSQSWG HFQNRVNLVGDIFRNDGSIMLOGVRES DGGNYTCSIHLGN  
LVFKKTIVLHVSPEEPRTLVT PAALRPLVLGGNQLV IIVGIVCATILLLPVLILIVK KTC  
GNKSSVNSTVLVKN TKTNPEIKEKPC HFERCEGEKHIYSPI IIVREVIEEEEPSEKSEAT  
YMTMHPVWPSLRSDRNNSLEKKSGGGMPKTQQAF

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**FIGURE 235**

TAAAACAGCTACAATATTCCAGGGCCAGTCACTTGCCATTTCTCATAACAGCGTCAGAGA  
GAAAGAACTGACTGAAACGTTTGAGATGAAGAAAGTTCTCCTCCTGATCACAGCCATCTT  
GGCAGTGGCTGTTGGTTTCCAGTCTCTCAAGACCAGGAACGAGAAAAAGAAGTATCAG  
TGACAGCGATGAATTAGCTTCAGGGTTTTTGTGTTCCCTTACCCATATCCATTTGCCC  
ACTTCCACCAATTCCATTTCCAAGATTTCCATGGTTTAGACGTAATTTTCCTATTCCAAT  
ACCTGAATCTGCCCCCTACAACTCCCCTTCCTAGCGAAAAGTAAACAAGAAGGATAAGTCA  
CGATAAACCTGGTCACCTGAAATTGAAATTGAGCCACTTCCTTGAAGAATCAAAATTCCT  
GTTAATAAAAGAAAAACAAATGTAATTGAAATAGCACACAGCATTCTCTAGTCAATATCT  
TTAGTGATCTTCTTTAATAAACATGAAAGCAAAGATTTTGTTTTCTTAATTTCCACA



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## FIGURE 236

MKKVLLLLITAILAVAVGFPVSQDQEREKRSISDSDELASGFFVFPYPYPFRPLPPIPFPR  
FPWFRRNFPIPIPIESAPTTPLPSEK

**Important features of the protein:**

**Signal peptide:**

amino acids 1-17

**Homologous region to B3-hordein:**

amino acids 47-85

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**FIGURE 237**

TCGCCATGGCCTCTGCCGGAATGCAGATCCTGGGAGTCGTCCTGACACTGCTGGGCTGGG  
TGAATGGCCTGGTCTCCTGTGCCCTGCCCATGTGGAAGGTGACCGCTTTCATCGGCAACA  
GCATCGTGGTGGCCCAGGTGGTGTGGGAGGGCCTGTGGATGTCCTGCGTGGTGCAGAGCA  
CCGCCAGATGCAGTGCAAGGTGTACGACTCACTGCTGGCGCTGCCACAGGACCTGCAGG  
CTGCACGTGCCCTCTGTGTCATCGCCCTCCTTGTGGCCCTGTTGCGCTTGCTGGTCTACC  
TTGCTGGGGCCAAGTGTACCACCTGTGTGGAGGAGAAGGATTCCAAGGCCCGCCTGGTGC  
TCACCTCTGGGATTGTCTTTGTCTCTCAGGGGTCTGACGCTAATCCCCGTGTGCTGGA  
CGGCGCATGCCATCATCCGGGACTTCTATAACCCCTGGTGGCTGAGGCCCAAAGCGGG  
AGCTGGGGGCCCTCCCTCTACTTGGGCTGGGCGGCCTCAGGCCTTTTGTGCTGGGTGGG  
GGTTGCTGTGCTGCACTTGCCCCCTCGGGGGGTCCCAGGGCCCCAGCCATTACATGGCCC  
GCTACTCAACATCTGCCCCCTGCCATCTCTCGGGGGCCCTCTGAGTACCCTACCAAGAATT  
ACGTCTGACGCTGGAGGGGAATGGGGGCTCCGCTGGCGCTAGAGCCATCCAGAAGTGGCAG  
TGCCCAACAGCTTTGGGATGGGTTCGTACCTTTTGTTCCTGCCTCCTGCTATTTTCTTT  
TGACTGAGGATATTTAAAATTCATTTGAAAACCTGAGCCAAGGTGTTGACTCAGACTCTCA  
CTTAGGCTCTGCTGTTTCTCACCCTTGATGATGGAGCCAAAGAGGGGATGCTTTGAGAT  
TCTGGATCTTGACATGCCCATCTTAGAAGCCAGTCAAGCTATGGAACATAATGCGGAGGCT  
GCTTGCTGTGCTGGCTTTGCAACAAGACAGACTGTCCCCAAGAGTTCCTGCTGCTGCTGG  
GGGCTGGGCTTCCCTAGATGTCACTGGACAGCTGCCCCCATCCTACTCAGGTCTCTGGA  
GCTCCTCTCTTCACCCCTGGAAAAACAAATCATCTGTTAACAAGGACTGCCACCTCCG  
GAACTTCTGACCTCTGTTTCCCTCCGTCTTGATAAGACGTCCACCCCCCAGGGCCAGGTCC  
CAGCTATGTAGACCCCCGCCCCACCTCCAACACTGCACCCTTCTGCCCTGCCCCCTCG  
TCTCACCCCTTTACACTCACATTTTATCAAATAAAGCATGTTTTGTTAGTGCA

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**FIGURE 238**

MASAGMQILGVVLTL LGWVNGLVSCALPMWKVTAFIGNSIVVAQVVWEGLWMSCVVQSTG  
QMCKVYDSL LALPQDLQAARALCVIALLVALFGLLVYLAGAKCTTCVEEKDSKARLVLT  
SGIVFVISGVLT LIPVCWTAHAIRDFYNPLVAEAQKREL GASLYLGWAASGLLLLGGL  
LCCTCPSGGSQG PSHYMARYSTSAP AISRGPSEYPTKNYV

**Transmembrane domains:**

amino acids 8-30 (type II), 82-102, 121-140, 166-186

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**FIGURE 239**

AGTGACAATCTCAGAGCAGCTTCTACACCACAGCCATTTCCAGCATGAAGATCACTGGGG  
GTCTCCTTCTGCTCTGTACAGTGGTCTATTTCTGTAGCAGCTCAGAAGCTGCTAGTCTGT  
CTCCAAAAAAGTGGACTGCAGCATTTACAAGAAGTATCCAGTGGTGGCCATCCCCTGCC  
CCATCACATACCTACCAGTTTGTGGTCTGACTACATCACCTATGGGAATGAATGTCACT  
TGTGTACCGAGAGCTTGAAAAGTAATGGAAGAGTTCAGTTTCTTCACGATGGAAGTTGCT  
AAATTCTCCATGGACATAGAGAGAAAGGAATGATATTCTCATCATCATCTTCATCATCCC  
AGGCTCTGACTGAGTTTCTTTCAGTTTACTGATGTTCTGGGTGGGGGACAGAGCCAGAT  
TCAGAGTAATCTTGACTGAATGGAGAAAGTTTCTGTGCTACCCCTACAAACCCATGCCTC  
ACTGACAGACCAGCATTTTTTTTTTAAACACGTCAATAAAAAAATAATCTCCAGA

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## FIGURE 240

MKITGGLLLLCTVVYFCSSSEAASLSPKKVDCSIYKKYPVVAIPCPITYLPVCGSDYITY  
GNECHLCTESLKSNGRVQFLHDGSC

Signal peptide:  
amino acids 1-19

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**FIGURE 241**

CCCGCGCCCGGTTCTCCCTCGCAGCACCTCGAAGTGCGCCCTCGCCCTCCTGCTCGCGC  
CCCGCGCCATGGCTGCCTCCCCGCGCGGCTGCTGTCCTGGCCCTGACCGGGCTGGCG  
CTGCTCCTGCTCCTGTGCTGGGGCCAGGTGGCATAAGTGGAAATAAACTCAAGCTGATG  
CTTCAAAAACGAGAAGCACCTGTTCCAATAAGACTAAAGTGGCCGTTGATGAGAATAAA  
GCCAAAGAATTCTTGGCAGCCTGAAGCGCCAGAAGCGGCAGCTGTGGGACCGGACTCGG  
CCCGAGGTGCAGCAGTGGTACCAGCAGTTTCTCTACATGGGCTTTGATGAAGCGAAATTT  
GAAGATGACATCACCTATTGGCTTAACAGAGATCGAAATGGACATGAATACTATGGCGAT  
TACTACCAACGTCACTATGATGAAGACTCTGCAATTGGTCCCCGAGCCCCCTACGGCTTT  
AGGCATGGAGCCAGCGTCAACTACGATGACTACTTACCATGACTTGCCACACGCTGTACA  
AGAAGCAAATAGCGATTCTCTTCATGTATCTCCTAATGCCTTACACTACTTGGTTTCTGA  
TTTGCTCTATTTACAGCAGATCTTTTCTACCTACTTTGTGTGATCAAAAAGAAGAGTTAA  
AACAAACACATGTAAATGCCTTTTGATATTTTCATGGGAATGCCTCTCATTTAAAAATAGAA  
ATAAAGCATTTTGTAAAAAGA

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## FIGURE 242

MAASPARPAVLALTGLALLLLLCWGPGGISGNKLLMLQKREAPVPTKTKVAVDENKAKE  
FLGSLKRQKRQLWDRTRPEVQQWYQQFLYMGFDEAKFEDDITYWLNDRNGHEYYGDDYQ  
RHYDEDSAIGPRSPYGFRRHGASVNYDDY

**Signal peptide:**  
amino acids 1-30

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**FIGURE 243**

CTCCATTAAACCACCACCAGCTCCCCAAGCCACCCCTTCAGCCATGAAGTTCCTGCTCCT  
GGTCTTGGCAGCCCTCGGATTCTTGACCCAGGTGATCCCAGCCAGTGCAGGTGGGTCAAA  
ATGTGTGAGTAACACCCCAGGATACTGCAGGACATGTTGCCACTGGGGGGAGACAGCATT  
GTTTCATGTGCAACGCTTCCAGAAAATGCTGCATCAGCTACTCCTTCTGCCGAAGCCTGA  
CCTACCACAGCTCATCGGTAACCACTGGCAATCAAGGAGAAGAAACACACAAAGGAAAGA  
CAAGAAGCAACAAACGACCGTAACATCATATAAACCCTGCTATCGCCTCCACCAACTCA  
GAGAAATATCATTTCCACAGTTCCAATTCCTCCTACATTGCTGAGTACTAGCCAAGGCTC  
CTCTTTATGGGGCAGATATCTATAGCCAACCCCAAACTTCTGTCTTCTATCATTCTGTC  
ATTCATCTAGTAACATAATTTGGAGTTTGTATCTATCTTACGAGAACAATCATCATGCAGA  
TTCGTCCACAGGGGATCTGTCAGTTTGGGTCTCCTCAAATGAAAAATGTCAAGACAGAATT  
GGACATGCAAAAGATTGACTGGGAGAACACACCTCTGATGGACAAAGGTGAGACAGAGCA  
GCCACAGGCAGGGAGAGCCTTCAGACTGCAACGCTGGCCTGATACGTGTCAAAGGAGAGA  
GGGATAGAGGAGGATTGAATAGAAGGAGACTAAGACTGCAGCTCTAAGAAAGTCTCAGCC  
AAACAGATGGGGAGGCCCAAAGCAAGGCTTGCCCCCTCAGAGGAGCTCACGCAGGGCAGGA  
ATAGCCAGGTTCTCATATCCCAGGGGTTGAGACTTGGCTGAGAACAGCCCCCTGGAGAACA  
TGGGGTGAAGTCTACCATAGGTCTGGAAGTATGAGGCTGTCCACCAACTATCCCCTTGAA  
GCAAGTTCTCTTGAAAGGAAATCTAAACAGTGCACCCCCATGGCTGCCACGGAGTATAAG  
GAGGGAGAGAAAGGAGCTGAAAGTCTAGGTTTGGCCAGCTAGGTAGACTGACTTGTGAGG  
TATTTATTTATTCATTTGAGTAACAAAGCAGACAGAATACATAGCCACCATTGGTAGTAC  
ACCCCAAAGCAAGGATGGCATGATGCTGGTGAAGTCAAAACGTGCCTACTCATGGTGTCAA  
ATTGGCATAATCCTCTTGGAAGCTGTGTGGAATAAGCACAGAGAAGCAGAACTCTAAT  
TGCTTAATCCACTAAACATTACTTCTGGGAATTGGCTCATCATAAATTATCCAAGAGAAA  
GCACAAAGTTATGGGCACAAAGGTTTTCCATATAATATTATTTAAATGCTGAGAAAATG  
AAAAAATCTAAATGGTGAAATATATACTAATGCCATCTATAAATAACAAATAAGATG  
TTTATAGAATAATGGAACATAATAACATTATTCAAAATTGCATTTATGCTATAGTTGTCA  
AAATTGTCTCCTTATATGATACAAAACATGAAAATTATGACTTTTTTGTGTTGGTTGGA  
AAGCAGAATTATGCATAAATTTCTTACAGTTCGATGCCCATTAGTTTTATATAACAT  
TTATTTGACACGTACTGACTTCTATCTGAGAAGAACAACCAAAACACTCAGGCCTAAAT  
AATTAAAAACGGTCTTAAAACTAGCAAACAGATAAGAAAAGATGTTAATGCCCATTC  
CTAACTTATGTCTTAGACCAAATTAATTCTAGATGGTTTTAAATGACAGTGTAAGT  
AAAGTATTAAAAGATTGTGTGGTCAAATATTCAATTTAAGAGCAAGGAAATCTTATAAA  
TATAACAATAGAGGCAGAACTCATGTAAGAATAAATTGATTAGGTGGTATTAAATATTAA  
GTTCTTATGTATGTCAAAGATATCATTTTGAATTCATCCATCTTATTGGGTATTGCAG  
GAGTTCATTCTTTTTTGTGTTATAAATACTCTCCGTATATGAATAGTATTCAATTTGTAT  
ACTGGTTTGTGATGGACATTTGGGTTGTTCCAGTTTATGGCTATTACAAATAAGCTT  
CTATGAACATTTATGTACA



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## FIGURE 244

MKFLLLVLAALGFLTQVIPASAGGSKCVSNTPGYCRTCCHWGETALFMCNASRKCCISYS  
FLPKPDLPLQLIGNHWQSRRTNTQRKDKKQQTTVTS

Important features of the protein:

Signal peptide:

amino acids 1-16

Transmembrane domain:

amino acids 1-22

N-glycosylation site:

amino acids 50-53

cAMP- and cGMP-dependent protein kinase phosphorylation site:

amino acids 79-82

N-myristoylation site:

amino acids 23-28

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**FIGURE 245**

GGAGAGAGGCGCGCGGGTGAAAGGCGCATTGATGCAGCCTGCGGCGGCCTCGGAGCGCGG  
CGGAGCCAGACGCTGACCACGTTCTCTCCTCGGTCTCCTCCGCCTCCAGCTCCGCGCTG  
CCCGGCAGCCGGGAGCCATGCGACCCCAGGGCCCCGCCGCCTCCCCGCAGCGGCTCCGCG  
GCCTCCTGCTGCTCCTGCTGCTGCAGCTGCCCGCGCCGTCGAGCGCCTCTGAGATCCCCA  
AGGGGAAGCAAAAGGCGCAGCTCCGGCAGAGGGAGGTGGTGGACCTGTATAATGGAATGT  
GCTTACAAGGGCCAGCAGGAGTGCCTGGTTCGAGACGGGAGCCCTGGGGCCAATGTTATTC  
CGGGTACACCTGGGATCCCAGGTTCGGGATGGATTCAAAGGAGAAAAGGGGGAATGTCTGA  
GGGAAAGCTTTGAGGAGTCCTGGACACCCAACTACAAGCAGTGTTTCATGGAGTTCATTGA  
ATTATGGCATAGATCTTGGGAAAATTGCGGAGTGTACATTTACAAAGATGCGTTCAAATA  
GTGCTCTAAGAGTTTTGTTTCAGTGGCTCACTTCGGCTAAAATGCAGAAATGCATGCTGTC  
AGCGTTGGTATTTTACATTCAATGGAGCTGAATGTTTCAGGACCTCTTCCCATTGAAGCTA  
TAATTTATTTGGACCAAGGAAGCCCTGAAATGAATTCAACAATTAATATTTCATCGCACTT  
CTTCTGTGGAAGGACTTTGTGAAGGAATTGGTGTCTGGATTAGTGGATGTTGCTATCTGGG  
TTGGCACTTGTTTCAGATTACCCAAAAGGAGATGCTTCTACTGGATGGAATTCAGTTTCTC  
GCATCATTATTGAAGAACTACCAAAATAAATGCTTTAATTTTCATTGCTACCTCTTTTT  
TTATTATGCCTTGGAATGGTTCACTTAAATGACATTTTAAATAAGTTTATGTATACATCT  
GAATGAAAAGCAAAGCTAAATATGTTTACAGACCAAAGTGTGATTTTCACTGTTTTTAA  
ATCTAGCATTATTCATTTTGCTTCAATCAAAGTGGTTTCAATATTTTTTTTAGTTGGTT  
AGAATACTTTCTTCATAGTCACATTCTCTCAACCTATAATTTGGAATATTGTTGTGGTCT  
TTTGTTTTTTCTCTTAGTATAGCATTTTTAAAAAATATAAAAGCTACCAATCTTTGTAC  
AATTTGTAAATGTTAAGAATTTTTTTTTATATCTGTAAATAAAAATTATTTCCAACA

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## FIGURE 246

MRPQGPAASPQRLRGLLLLLLLQLPAPSSASEIPKGKQKAQLRQREVVDLYNGMCLQGPA  
GVPGRDGSPGANVIPGTPGIPGRDGFKEKGECLRESFEESWTPNYKQCSWSSLNYGIDL  
GKIAECTFTKMRSNSALRVLFSGSLRLKCRNACCQRWYFTFNGAECGPLPIEAIYLDQ  
GSPEMNSTINIHRTSSVEGLCEGIGAGLVDVAIWVGTCSDYPKGDASTGWNSVSRIIEE  
LPK

**Signal peptide:**  
amino acids 1-30

**Transmembrane domain:**  
amino acids 195-217

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**FIGURE 247**

GGCCGTTGGTTGGTGC GCGGCTGAAGGGTGTGGCGCGAGCAGCGTCGTTGGTTGGCCGGC  
GGCGGGCCGGGACGGGCATGGCCCTGCTGCTGTGCCTGGTGTGCCTGACGGCGGCGCTGG  
CCCACGGCTGTCTGCACTGCCACAGCAACTTCTCCAAGAAGTTCTCCTTCTACCGCCACC  
ATGTGAACTTCAAGTCCTGGTGGGTGGGCGACATCCCCGTGTCAGGGGCGCTGCTCACCG  
ACTGGAGCGACGACACGATGAAGGAGCTGCACCTGGCCATCCCCGCCAAGATCACCCGGG  
AGAAGCTGGACCAAGTGGCGACAGCAGTGTACCAGATGATGGATCAGCTGTACCAGGGGA  
AGATGTACTTCCCCGGGTATTTCCCCAACGAGCTGCGAAACATCTTCCGGGAGCAGGTGC  
ACCTCATCCAGAACGCCATCATCGAAAGGCACCTGGCACCAGGCAGCTGGGGAGGAGGGC  
AGCTCTCCAGGGAGGGACCCAGCCTAGCACCTGAAGGATCAATGCCATCACCCCGCGGGG  
ACCTCCCCCTAAGTAGCCCCCAGAGGCGCTGGGAGTGTGTCACCGCCCTCCCCTGAAGTT  
TGCTCCATCTCACGCTGGGGGTCAACCTGGGGACCCCTTCCCTCCGGGCCATGGACACAC  
ATACATGAAAACCAGGCCGCATCGACTGTGTCAGCACCGCTGTGGCATCTTCCAGTACGAGA  
CCATCTCCTGCAACAACTGCACAGACTCGCACGTGCGCTGCTTTGGCTATAACTGCGAGT  
AGGGCTCAGGCATCACACCCACCCGTGCCAGGGCCCTACTGTCCCTGGGGTCCCAGGCTC  
TCCTTGAGGGGGGCTCCCCGCCTTCCACCTGGCTGTGTCAGGGTAGGGCGGGGCCGTGGG  
TTCAGGGGCGCACCACTTCCAAGCCTGTGTCCACAGGTCCTCGGCGCAGTGGAAGTCAG  
CTGTCCAGGGCCTCCTGAACTACATAAATAACTGGCACAAAGTAAGTCCCCTCCTCAAACC  
AACACAGGCAGTGTGTGTATGTGAGCACCTCGTGGGTGAGTATGTGTGGGGCACAGGCTG  
GCTCCCTCAGCTCCCACGTCTTAGAGGGGCTCCCGAGGAGGTGGAACCTCAACCCAGCTC  
TGCGCAGGAGGCGGCTGCAGTCCTTTTCTCCCTCAAAGGTCTCCGACCCTCAGCTGGAGG  
CGGGCATCTTTCCTAAAGGGTCCCCATAGGGTCTGGTTCCACCCCATCCCAGGTCTGTGG  
TCAGAGCCTGGGAGGGTTCCCTACGATGGTTAGGGGTGCCCCATGGAGGGGCTGACTGCC  
CCACATTGCCTTTCAGACAGGACACGAGCATGAGGTAAGGCCGCCCTGACCTGGACTTCA  
GGGGGAGGGGGTAAAGGGAGAGAGGAGGGGGGCTAGGGGGTCTCTAGATCAGTGGGGGC  
ACTGCAGGTGGGGCTCTCCCTATACCTGGGACACCTGCTGGATGTCACCTCTGCAACCAC  
ACCCATGTGGTGGTTTCATGAACAGACCACGCTCCTCTGCCTTCTCCTGGCCTGGGACAC  
ACAGAGCCACCCCGGCCTTGTGAGTGACCCAGAGAAGGGAGGCCTCGGGAGAAGGGGTGC  
TCGTAAGCCAAACACCAGCGTGCCGCGGCCTGCACACCCTTCGGACATCCCAGGCACGAGG  
GTGTCGTGGATGTGGCCACACATAGGACCACACGTCCCAGCTGGGAGGAGAGGCCTGGGG  
CCCCCAGGGAGGGAGGCAGGGGGTGGGGGACATGGAGAGCTGAGGCAGCCTCGTCTCCCC  
GCAGCCTGGTATCGCCAGCCTTAAGGTGTCTGGAGCCCCCACACTTGGCCAACCTGACCT  
TGGAAGATGCTGCTGAGTGTCTCAAGCAGCACTGACAGCAGCTGGGCCTGCCCCAGGGCA  
ACGTGGGGGCGGAGACTCAGCTGGACAGCCCCTGCCTGTCACTCTGGAGCTGGGCTGCTG  
CTGCCTCAGGACCCCTCTCCGACCCCGGACAGAGCTGAGCTGGCCAGGGCCAGGAGGGC  
GGGAGGGAGGGAATGGGGGTGGGCTGTGCGCAGCATCAGCGCCTGGGCAGGTCCGCAGAG  
CTGCGGGATGTGATTAAAGTCCCTGATGTTTCTC

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## FIGURE 248

MALLLCVLCLTAALAHGCLHCHSNFSKKFSFYRHHVNFKSWWVGDI PVSGALLTDWSDDT  
MKELHLAIPAKITREKLDQVATAVYQMDQLYQGKMYFFGYFPNELRNI FREQVHLIQNA  
I IERHLAPGSWGGGQLSREGPSLAPEGSMPSPRGDL P

Signal peptide:  
amino acids 1-15

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**FIGURE 249**

CGACGATGCTACGCGCGCCCGGCTGCCTCCTCCGGACCTCCGTAGCGCCTGCCGCGGCCC  
TGGCTGCGGCGCTGCTCTCGTCGCTTGCGCGCTGCTCTCTTCTAGAGCCGAGGGACCCGG  
TGGCCTCGTCGCTCAGCCCCTATTTCGGCACCAAGACTCGCTACGAGGATGTCAACCCCG  
TGCTATTGTGCGGCCCCGAGGCTCCGTGGCGGGACCCCTGAGCTGCTGGAGGGGACCTGCA  
CCCCGGTGACGCTGGTCGCCCTCATTGCCACGGCACCCGCTACCCACGGTCAAACAGA  
TCCGCAAGCTGAGGCAGCTGCACGGGTTGCTGCAGGCCCGCGGGTCCAGGGATGGCGGGG  
CTAGTAGTACCGGCAGCCGCGACCTGGGTGCAGCGCTGGCCGACTGGCCTTTGTGGTACG  
CGGACTGGATGGACGGGCAGCTAGTAGAGAAGGGACGGCAGGATATGCGACAGCTGGCGC  
TGCGTCTGGCCTCGCTCTTCCCGGCCCTTTTCAGCCGTGAGAACTACGGCCGCGCTGCGGC  
TCATCACCAGTTCCAAGCACCGCTGCATGGATAGCAGCGCCGCGCTTCTGACAGGGGCTGT  
GGCAGCACTACCACCCTGGCTTGCCGCCGCGGACGTGCGAGATATGGAGTTTGGACCTC  
CAACAGTTAATGATAAACTAATGAGATTTTTTGATCACTGTGAGAAGTTTTTAACTGAAG  
TAGAAAAAATGCTACAGCTCTTTATCACGTGGAAGCCTTCAAACTGGACCAGAAATGC  
AGAACATTTTAAAAAAGTTGCAGCTACTTTGCAAGTGCCAGTAAATGATTTAAATGCAG  
ATTTAATTCAAGTAGCCTTTTTCACCTGTTTCAATTTGACCTGGCAATTAAAGGTGTTAAAT  
CTCCTTGGTGTGATGTTTTTGACATAGATGATGCAAAGGTATTAGAATATTTAAATGATC  
TGAAACAATATTGGAAAAGAGGATATGGGTATACTATTAAACAGTCGATCCAGCTGCACCT  
TGTTTTCAGGATATCTTTCAGCACTTGGACAAAGCAGTTGAACAGAAACAAAGGTCTCAGC  
CAATTTCTTCTCCAGTCATCCTCCAGTTTGGTCATGCAGAGACTCTTCTTCCACTGCTTT  
CTCTCATGGGCTACTTCAAAGACAAGGAACCCCTAACAGCGTACAATTACAAAAACAAA  
TGCATCGGAAGTTCGGAAGTGGTCTCATTGTACCTTATGCCTCGAACCTGATATTTGTGC  
TTTACCACTGTGAAAATGCTAAGACTCCTAAAGAACAAATCCGAGTGCAGATGTTATTAA  
ATGAAAAGGTGTTACCTTTGGCTTACTCACAAGAACTGTTTCATTTTATGAAGATCTGA  
AGAACCACTACAAGGACATCCTTCAGAGTTGTCAAACAGTGAAGAATGTGAATTAGCAA  
GGGCTAACAGTACATCTGATGAACTATGAGTAAGTAACTGAAGAACATTTTTAATTCTTTAGGA  
ATCTGCAATGAGTGATTACATGCTTGTAAATAGGTAGGCAATTCCTTGATTACAGGAAGCT  
TTTATATTACTTGAGTATTTCTGTCTTTTTCACAGAAAAACATTGGGTTTCTCTCTGGGTT  
TGGACATGAAATGTAAGAAAAGATTTTTTCACTGGAGCAGCTCTCTTAAGGAGAAACAAAT  
CTATTTAGAGAAACAGCTGGCCCTGCAATGTTTACAGAAATGAAATTCCTTCTACTTAT  
ATAAGAAATCTCACACTGAGATAGAATTGTGATTTTATAATAACACTTGAAAAGTGCTGG  
AGTAACAAAATATCTCAGTTGGACCATCCTTAACCTTGATTGAACTGTCTAGGAACCTTAC  
AGATTGTTCTGCAGTTCTCTCTTCTTTTCTCAGGTAGGACAGCTCTAGCATTTTCTTAA  
TCAGGAATATTGTGGTAAGCTGGGAGTATCACTCTGGAAGAAAGTAACATCTCCAGATGA  
GAATTTGAAACAAGAAACAGAGTGTTGTAAGGACACCTTCACTGAAGCAAGTCGGAAA  
GTACAATGAAAATAAATATTTTTTGGTATTTATTTATGAAATATTTGAACATTTTTTCAAT  
AATTCCTTTTTTACTTCTAGGAAGTCTCAAAGACCATCTTAAATTATTATATGTTTGGAC  
AATTAGCAACAAGTCAGATAGTTAGAATCGAAGTTTTTCAAATCCATTGCTTAGCTAACT  
TTTTTCAATCTGTCACTTGGCTTCGATTTTTATATTTTCTATTATATGAAATGTATCTTT  
TGGTTGTTTGATTTTTTCTTTCTTTCTTTGTAAATAGTTCTGAGTTCTGTCAAATGCCGTG  
AAAGTATTTGCTATAATAAAGAAAATCCTTGTGACTTTAAAAA

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**FIGURE 250**

MLRAPGCLLRTSVAPAAALAAALLSSLARCSLLEPRDPVASSLSFYFGTKTRYEDVNPVL  
LSGPEAPWRDPELLEGTCTPVQLVALIRHGTRYPTVKQIRKLRQLHGLLQARGSRDGGAS  
STGSRDLGAALADWPLWYADWMDGQLVEKGRQDMRQLALRLASLFPALFSRENYGRLRLI  
TSSKHRCMDSSAAFLQGLWQHYPGLPPPVDADMEFGPPTVNDKLMRFFDHCEKFLTEVE  
KNATALYHVEAFKTGPEMQNILKKVAATLQVPVNDLNADLIQVAFFTCSFDLAIKGVKSP  
WCDVFDIDDAKVLEYLNDLKQYWKRGYGYTINSRSSCTLFQDIFQHLDKAVEQKQRSQPI  
SSPVILQFGHAETLLPLLSLMGYFKDKEPLTAYNYKKQMRKFRSGLIVPYASNLI FVLY  
HCENAKTPKEQFRVQMLLNEKVLPLAYSQETVSFYEDLKNHYKDILQSCQTSEECELARA  
NSTSDEL

**Important features:****Signal sequence**

amino acids 1-30

**N-glycosylation sites:**

amino acids 242-246, 481-485

**N-myristoylation sites.**

amino acids 107-113, 113-119, 117-123, 118-124, 128-134

**Endoplasmic reticulum targeting sequence:**

amino acids 484-489

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**FIGURE 251**

GGAGAGCCGCGGCTGGGACCGGAGTGGGGAGCGCGGCGTGGAGGTGCCACCCGCGCGGG  
TGGCGGAGAGATCAGAAGCCTCTTCCCCAAGCCGAGCCAACCTCAGCGGGGACCCGGGCT  
CAGGGACGCGGCGGCGGCGGCGGCGGCGACTGCAGTGGCTGGACGATGGCAGCGTCCGCCGGA  
GCCGGGGCGGTGATTGCAGCCCCAGACAGCCGGCGCTGGCTGTGGTGGTGGTGGCGGCG  
GCGCTTGGGCTCTTGACAGCTGGAGTATCAGCCTTGGAAGTATATACGCCAAAAGAAATC  
TTCGTGGCAAATGGTACACAAGGGAAGCTGACCTGCAAGTTCAAGTCTACTAGTACGACT  
GGCGGGTTGACCTCAGTCTCCTGGAGCTTCCAGCCAGAGGGGGCCGACACTACTGTGTCTG  
TTTTTCCACTACTCCCAAGGGCAAGTGTACCTTGGGAATTATCCACCATTAAAGACAGA  
ATCAGCTGGGCTGGGACCTTGACAAGAAAGATGCATCAATCAACATAGAAAATATGCAG  
TTTATACACAATGGCACCTATATCTGTGATGTCAAAAACCCTCCTGACATCGTTGTCCAG  
CCTGGACACATTAGGCTCTATGTCTAGAAAAAGAGAATTTGCCTGTGTTTCCAGTTTGG  
GTAGTGGTGGGCATAGTTACTGCTGTGGTCTAGGTCTCACTCTGCTCATCAGCATGATT  
CTGGCTGTCTCTATAGAAGGAAAACTCTAAACGGGATTACACTGGCTGCAGTACATCA  
GAGAGTTTGTCAACAGTTAAGCAGGCTCCTCGGAAGTCCCCCTCCGACACTGAGGGTCTT  
GTAAAGAGTCTGCCTTCTGGATCTCACCAGGGCCCAGTCATATATGCACAGTTAGACCAC  
TCCGGCGGACATCACAGTGACAAGATTAACAAGTCAGAGTCTGTGGTGTATGCGGATATC  
CGAAAGAATTAAAGAGAATACCTAGAACATATCCTCAGCAAGAAACAAAACCAAACTGGAC  
TCTCGTGCAGAAAATGTAGCCCATTACCACATGTAGCCTTGGAGACCCAGGCAAGGACAA  
GTACACGTGTACTCACAGAGGGAGAGAAAGATGTGTACAAAGGATATGTATAAATATTCT  
ATTTAGTCATCCTGATATGAGGAGCCAGTGTTCATGATGAAAAGATGGTATGATTCTAC  
ATATGTACCCATTGTCTTGCTGTTTTTGTACTTTCTTTTCAGGTCAATTTACAATTGGGAG  
ATTTCAGAAACATTCCTTTCACCATCATTTAGAAATGGTTTGCCTTAATGGAGACAATAG  
CAGATCCTGTAGTATTTCCAGTAGACATGGCCTTTTAATCTAAGGGCTTAAGACTGATTA  
GTCTTAGCATTACTGTAGTTGGAGGATGGAGATGCTATGATGGAAGCATAACCCAGGGTG  
GCCTTTAGCACAGTATCAGTACCATTTATTTGTCTGCCGCTTTTAAAAAATACCCATTGG  
CTATGCCACTTGAAAACAATTTGAGAAGTTTTTTTGAAGTTTTTCTCACTAAAATATGGG  
GCAATTGTTAGCCTTACATGTTGTGTAGACTTACTTTAAGTTTGCACCCTTGAAATGTGT  
CATATCAATTTCTGGATTATAATAGCAAGATTAGCAAAGGATAAATGCCGAAGGTCAT  
TCATTCTGGACACAGTTGGATCAATACTGATTAAGTAGAAAAATCCAAGCTTTGCTTGAGA  
ACTTTTGTAACGTGGAGAGTAAAAAGTATCGGTTTTA



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**FIGURE 252**

MAASAGAGAVIAAPDSRRWLWSVLAAALGLLTAGVSALEVYTPKEIFVANGTQGKLTCKF  
KSTSTTGGLTSVSWSFQPEGADTTVSFFHYSQGQVYLGNYPPFKDRISWAGDLDDKSDASI  
NIENMQFIHNGTYICDVKNPPDIVVQPGHIRLYVVEKENLPVFPVWVVVGIVTAVVLGLT  
LLISMILAVLYRRKNSKRDTGCTSESLSPVKQAPRKSPDTEGLVKSLPSGSHQGPVI  
YAQLDHSGGHHSDKINKSESVVYADIRKN

**Signal peptide:**  
amino acids 1-37

**Transmembrane domain:**  
amino acids 161-183

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**FIGURE 253**

GTGACACTATAGAAGAGCTATGACGTGCGCATGCACGCGTACGTAAGCTCGGAATTCGGCT  
CGAGGCTGGTGGGAAGAAGCCGAGATGGCGGCAGCCAGCGCTGGGGCAACCCGGCTGCTC  
CTGCTCTTGCTGATGGCGGTAGCAGCGCCAGTCGAGCCCGGGCAGCGGCTGCCGGGCC  
GGGACTGGTGC CGAGGGGCTGGGGCGGAAGGTCGAGAGGGCGAGGCCTGTGGCACGGTG  
GGGCTGCTGCTGGAGCACTCATTTGAGATCGATGACAGTGCCAACTTCCGGAAGCGGGGC  
TCACTGCTCTGGAACCAGCAGGATGGTACCTTGTCCCTGTCACAGCGGCAGCTCAGCGAG  
GAGGAGCGGGGCCGACTCCGGGATGTGGCAGCCCTGAATGGCCTGTACCGGGTCCGGATC  
CCAAGGCGACCCGGGGCCCTGGATGGCCTGGAAGCTGGTGGCTATGTCTCCTCCTTTGTC  
CCTGCGTGCTCCCTGGTGGAGTCGCACCTGTCGGACCAGCTGACCCTGCACGTGGATGTG  
GCCGGCAACGTGGTGGGCGTGTCGGTGGTGACGCACCCCGGGGGCTGCCGGGGCCATGAG  
GTGGAGGACGTGGACCTGGAGCTGTTCAACACCTCGGTGCAGCTGCAGCCGCCACCACA  
GCCCCAGGCCCTGAGACGGCGGCCTTCATTGAGCGCCTGGAGATGGAACAGGCCCAGAAG  
GCCAAGAACCCCCAGGAGCAGAAGTCCTTCTTCGCCAAATACTGGATGTACATCATTCCC  
GTCGTCCTGTTCTCATGATGTCAGGAGCGCCAGACACCGGGGGCCAGGGTGGGGGTGGG  
GGTGGGGGTGGTGGTGGGGGTAGTGGCCTTTGCTGTGTGCCACCCCTCCCTGTAAGTCTAT  
TAAAAACATCGACGATACATTGAAATGTGTGAACGTTTTGAAAAGCTACAGCTTCCAGC  
AGCCAAAAGCAACTGTTGTTTTGGCAAGACGGTCCTGATGTACAAGCTTGATTGAAATTC  
ACTGCTCACTTGATACGTTATTCAGAAACCAAGGAATGGCTGTCCCCATCCTCATGTGG  
CTGTGTGGAGCTCAGCTGTGTTGTGTGGCAGTTTATTAACTGTCCCCAGATCGACACG  
CAAAAAAAAA

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**FIGURE 254**

MAAASAGATRLLLLLLMAVAAPSRARGSGCRAGTGARGAGAEGREGEACGTVGLLLEHSF  
EIDDSANFRKRGSLLWNQQDGTLSLSQRQLSEEERGLRDVAALNGLYRVRI PRRP GALT  
GLEAGGYVSSFVPACSLVESHLS DQLTLHVDVAGNVVGVSVVTHPGGCRGHEVEDVDLEL  
FNTSVQLQPPTTAPGPETA AFIERLEMEQAQKAKNPQEQKSFFAKYWMYIIPVVLFLMMS  
GAPDTGGQGGGGGGGGGGSGSLCCVPPSL

**Signal peptide:**  
amino acids 1-24

**Transmembrane domain:**  
amino acids 226-243

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**FIGURE 255**

GCGACGCGCGGGCGGGGCGGCGAGAGGAAACGCGGCGCCGGGCGGGCCCGGCCCTGGAGA  
TGGTCCCCGCGCGCGGGCTGGTGTGTCTCGTGCTCTGGCTCCCCGCGTGCGTCCGCGG  
CCCACGGCTTCCGTATCCATGATTATTTGTACTTTCAAGTGCTGAGTCCTGGGGACATTC  
GATACATCTTCACAGCCACACCTGCCAAGGACTTTGGTGGTATCTTTCACACAAGGTATG  
AGCAGATTACCTTGTCCCCGCTGAACCTCCAGAGGCCTGCGGGGAACTCAGCAACGGTT  
TCTTCATCCAGGACCAGATTGCTCTGGTGGAGAGGGGGGGCTGCTCCTTCCTCTCCAAGA  
CTCGGTGGTCCAGGAGCACGGCGGGCGGGCGGTGATCATCTCTGACAACGCAGTTGACA  
ATGACAGCTTCTACGTGGAGATGATCCAGGACAGTACCCAGCGCACAGCTGACATCCCCG  
CCCTCTTCCTGCTCGGCCGAGACGGCTACATGATCCGCCGCTCTCTGGAACAGCATGGGC  
TGCCATGGGCCATCATTTCCATCCCAGTCAATGTCACCAGCATCCCCACCTTTGAGCTGC  
TGCAACCGCCCTGGACCTTCTGGTAGAAAGAGTTTGTCCACATTCCAGCCATAAGTGACT  
CTGAGCTGGGAAGGGGAAACCCAGGAATTTTGCTACTTGGAATTTGGAGATAGCATCTGG  
GGACAAGTGGAGCCAGGTAGAGGAAAAGGGTTTGGGCGTTGCTAGGCTGAAAGGGAAGCC  
ACACCACTGGCCTTCCCTTCCCCAGGGCCCCCAAGGGTGTCTCATGCTACAAGAAGAGGC  
AAGAGACAGGCCCCAGGGCTTCTGGCTAGAACCCGAAACAAAAGGAGCTGAAGGCAGGTG  
GCCTGAGAGCCATCTGTGACCTGTCACACTCACCTGGCTCCAGCCTCCCCTACCCAGGGT  
CTCTGCACAGTGACCTTCACAGCAGTTGTTGGAGTGGTTTAAAGAGCTGGTGTTTGGGGA  
CTCAATAAACCTCACTGACTTTTTAGCAATAAAGCTTCTCATCAGGGTTGCAAAAAAA  
AAAAAAAAAAAAAAAAAAAA

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## FIGURE 256

MVPGAAGWCCLVLWLPACVAAHGFRIDYLYFQVLSPGDIRYIFTATPAKDFGGIFHTRY  
EQIHLVPAEPPEACGELSNGFFIQDQIALVERGGCSFLSKTRVVQEHGGRAVIIISDNAV  
NDSFYVEMIQDSTQRTADIPALFLLGRDGYMIRRSLEQHGLPWAIISIPVNVTSIPTFEL  
LQPPWTFW

Signal peptide:  
amino acids 1-20

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**FIGURE 257**

CTCGCTTCTTCCTTCTGGATGGGGGCCCAGGGGGCCCAGGAGAGTATAAAGGCGATGTGG  
AGGGTGCCCGGCACAACCAGACGCCCAGTCACAGGCGAGAGCCCTGGGATGCACCGGCCA  
GAGGCCATGCTGCTGCTGCTCACGCTTGCCCTCCTGGGGGGCCCCACCTGGGCAGGGAAG  
ATGTATGGCCCTGGAGGAGGCAAGTATTTTCAGCACCACTGAAGACTACGACCATGAAATC  
ACAGGGCTGCGGGTGTCTGTAGGTCTTCTCCTGGTGAAAAGTGTCAGGTGAAACTTGGA  
GACTCCTGGGACGTGAAACTGGGAGCCTTAGGTGGGAATACCCAGGAAGTCACCCTGCAG  
CCAGGCGAATACATCACAAAAGTCTTTGTGCGCTTCCAAGCTTTCCTCCGGGGTATGGTC  
ATGTACACCAGCAAGGACCGCTATTTCTATTTTGGGAAGCTTGATGGCCAGATCTCCTCT  
GCCTACCCAGCCAAGAGGGGCAGGTGCTGGTGGGCATCTATGGCCAGTATCAACTCCTT  
GGCATCAAGAGCATTGGCTTTGAATGGAATTATCCACTAGAGGAGCCGACCACTGAGCCA  
CCAGTTAATCTCACATACTCAGCAAACCTACCCGTGGGTGCGTAGGGTGGGGTATGGGGC  
CATCCGAGCTGAGGCCATCTGTGTGGTGGTGGCTGATGGTACTGGAGTAACTGAGTCGGG  
ACGCTGAATCTGAATCCACCAATAAATAAAGCTTCTGCAGAAAA

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**FIGURE 258**

MHRPEAMLLLLTLALLGGPTWAGKMYGPGGGKYFSTTEDYDHEITGLRVSVGLLLVKSQ  
VKLGDSWDVKLGALGGNTQEVTLQPGYITKVFAFQAFLRGMVMTSKDRYFYFGKLDG  
QISSAYPSQEGQVLVGIYGQYQLLGIKSIGFEWNYPLEEPTTEPPVNLTYSANSPVGR

**Signal peptide:**  
amino acids 1-22

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**FIGURE 259**

CAGACATGGCTCAGTCACTGGCTCTGAGCCTCCTTATCCTGGTTCTGGCCTTTGGCATCC  
CCAGGACCCAAGGCAGTGATGGAGGGGCTCAGGACTGTTGCCTCAAGTACAGCCAAAGGA  
AGATTCCCGCCAAGGTTGTCCGCAGCTACCGGAAGCAGGAACCAAGCTTAGGCTGCTCCA  
TCCCAGCTATCCTGTTCTTGCCCCGCAAGCGCTCTCAGGCAGAGCTATGTGCAGACCCAA  
AGGAGCTCTGGGTGCAGCAGCTGATGCAGCATCTGGACAAGACACCATCCCCACAGAAAC  
CAGCCCAGGGCTGCAGGAAGGACAGGGGGGCTCCAAGACTGGCAAGAAAGGAAAGGGCT  
CCAAAGGCTGCAAGAGGACTGAGCGGTCACAGACCCCTAAAGGGCCATAGCCCAGTGAGC  
AGCCTGGAGCCCTGGAGACCCACACAGCCTCACCAGCGCTTGAAGCCTGAACCCAAGATG  
CAAGAAGGAGGCTATGCTCAGGGGCCCTGGAGCAGCCACCCCATGCTGGCCTTGCCACAC  
TCTTTCTCCTGCTTTAACCACCCCATCTGCATTCCCAGCTCTACCCTGCATGGCTGAGCT  
GCCCACAGCAGGCCAGGTCCAGAGAGACCGAGGAGGGAGAGTCTCCCAGGGAGCATGAGA  
GGAGGCAGCAGGACTGTCCCCTTGAAGGAGAATCATCAGGACCCTGGACCTGATACGGCT  
CCCCAGTACACCCACCTCTTCCTTGTAATATGATTTATACCTAACTGAATAAAAAGCT  
GTTCTGTCTTCCCNCCCA



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## FIGURE 260

MAQSLALSLLILVLAFGIPTQGS DGG A QDCCLKYSQRKIPAKVVRSYRKQEPSLGCSIP  
AILFLPRKRSQAELCADPKELWVQQLMQHLDKTPSPQKPAQGCRKDRGASKTGKKGKGSK  
GCKRTERSQTPKGP

**Important features of the protein:**

**Signal peptide:**

amino acids 1-17

**cAMP- and cGMP-dependent protein kinase phosphorylation site:**

amino acids 67-71

**N-myristoylation sites:**

amino acids 17-23, 23-29, 27-33, 108-114, 118-124, 121-127

**Amidation site:**

amino acids 112-116

**Small cytokines:**

amino acids 51-91

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**FIGURE 261**

GGGACTACAAGCCGCGCCGCGCTGCCGCTGGCCCCCTCAGCAACCCCTCGACATGGCGCTGA  
GGCGGCCACCGCGACTCCGGCTCTGCGCTCGGCTGCCTGACTTCTTCCTGCTGCTGCTTT  
TCAGGGGCTGCCTGATAGGGGCTGTAAATCTCAAATCCAGCAATCGAACCCAGTGGTAC  
AGGAATTTGAAAGTGTGGAAGTGTCTTGCATCATTACGGATTTCGAGACAAGTGACCCCA  
GGATCGAGTGGAAGAAAATTCAAGATGAACAAACCACATATGTGTTTTTTTGACAACAAAA  
TTCAGGGGAGACTTGGCGGGTCGTGCAGAAATACTGGGGAAGACATCCCTGAAGATCTGGA  
ATGTGACACGGAGAGACTCAGCCCTTTATCGCTGTGAGGTCGTTGCTCGAAATGACCGCA  
AGGAAATTGATGAGATTGTGATCGAGTTAACTGTGCAAGTGAAGCCAGTGACCCCTGTCT  
GTAGAGTGCCGAAGGCTGTACCAGTAGGCAAGATGGCAACACTGCACTGCCAGGAGAGTG  
AGGGCCACCCCGGCTCACTACAGCTGGTATCGCAATGATGTACCACTGCCACGGATT  
CCAGAGCCAATCCAGATTTCGCAATCTTCTTTCCACTTAACTCTGAAACAGGCACTT  
TGGTGTTCACTGCTGTTTACAAGGACGACTCTGGGCAGTACTACTGCATTGCTTCCAATG  
ACGCAGGCTCAGCCAGGTGTGAGGAGCAGGAGATGGAAGTCTATGACCTGAACATTGGCG  
GAATTATTGGGGGGTCTGGTTGTCTTGTCTGTACTGGCCCTGATCACGTTGGGCATCT  
GCTGTGCATACAGACGTGGCTACTTCATCAACAATAAACAGGATGGAGAAAGTTACAAGA  
ACCCAGGGAACAGATGGAGTTAACTACATCCGCACTGACGAGGAGGGCGACTTCAGAC  
ACAAGTCATCGTTTGTGATCTGAGACCCGCGGTGTGGCTGAGAGCGCACAGAGCGCACGT  
GCACATACCTCTGCTAGAACTCCTGTCAAGGCAGCGAGAGCTGATGCACTCGGACAGAG  
CTAGACACTCATTCAGAAGCTTTTCGTTTTGGCCAAAGTTGACCACTACTCTTCTTACTC  
TAACAAGCCACATGAATAGAAGAATTTTCTCAAGATGGACCCGGTAAATATAACCACAA  
GGAAGCGAACTGGGTGCGTTCACTGAGTTGGGTTCTTAATCTGTTTCTGGCCTGATTCC  
CGCATGAGTATTAGGGTGATCTTAAAGAGTTTGCTCACGTAAACGCCCGTGCTGGGCCCT  
GTGAAGCCAGCATGTTTACCACCTGGTCGTTTCCAGCAGCCACGACAGCACCATGTGAGATGG  
CGAGGTGGCTGGACAGCACCAGCAGCGCATCCCGCGGGAACCCAGAAAAGGCTTCTTAC  
ACAGCAGCCTTACTTCATCGGCCACAGACACCACCGCAGTTTCTTCTTAAAGGCTCTGC  
TGATCGGTGTTGCAGTGTCCATTGTGGAGAAGCTTTTTTGGATCAGCATTTTTGTAAAAACA  
ACCAAAATCAGGAAGGTAAATTGGTTGCTGGAAGAGGGATCTTGCTGAGGAACCTGCT  
TGTTCAACAGGGTGTGAGATTAAAGGAAAACCTTCGTCTTAGGCTAAGTCTGAAATGGT  
ACTGAAATATGCTTTTTCTATGGGTCTTGTTTATTTTATAAAATTTTACATCTAAATTTTT  
GCTAAGGATGTATTTTGATTATTGAAAAGAAAATTTCTATTTAACTGTAAATATATTGT  
CATACAATGTTAAATAACCTATTTTTTTTAAAAAGTTCAACTTAAGGTAGAAGTTCCAAG  
CTACTAGTGTTAAATTGGAAAATATCAATAATTAAGAGTATTTTACCCAAGGAATCCTCT  
CATGGAAGTTTACTGTGATGTTCTTTTTCTCACACAAGTTTTAGCCTTTTTTACAAGGGA  
ACTCATACTGTCTACACATCAGACCATAGTTGCTTAGGAAACCTTTAAAAATTCAGTTA  
AGCAATGTTGAAATCAGTTTGCATCTCTTCAAAAGAAACCTCTCAGGTTAGCTTTGAACT  
GCCTCTTCTGAGATGACTAGGACAGTCTGTACCCAGAGGCCACCCAGAAGCCCTCAGAT  
GTACATACACAGATGCCAGTCAGCTCCTGGGGTTGCGCCAGGCGCCCCGCTCTAGCTCA  
CTGTTGCTCGCTGTCTGCCAGGAGGCCCTGCCATCCTTGGGCCCTGGCAGTGGCTGTGT  
CCCAGTGAGCTTTACTCACGTGGCCCTTGCTTCATCCAGCACAGCTCTCAGGTGGGCACT  
GCAGGGACACTGGTGTCTTCCATGTAGCGTCCCAGCTTTGGGCTCCTGTAACAGACCTCT  
TTTTGGTTATGGATGGCTCACAAAATAGGGCCCCCAATGCTATTTTTTTTTTTTAAAGTTT  
GTTTAATTATTTGTTAAGATTGTCTAAGGCCAAAGGCAATTGCGAAATCAAGTCTGTCAA  
GTACAATAACATTTTTTAAAGAAAATGGATCCCACTGTTCTCTTTGCCACAGAGAAAGC  
ACCCAGACGCCACAGGCTCTGTGCGATTTCAAAACAAACCATGATGGAGTGGCGGCCAGT  
CCAGCCTTTTAAAGAACGTGAGGTGGAGCAGCCAGGTGAAAGGCCTGGCGGGGAGGAAAG  
TGAAACGCCTGAATCAAAGCAGTTTTCTAATTTTGACTTTAAATTTTTTCATCCGCCGGA

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GACACTGCTCCCATTTTGTGGGGGGACATTAGCAACATCACTCAGAAGCCTGTGTTCTTCA  
AGAGCAGGTGTTCTCAGCCTCACATGCCCTGCCGTGCTGGACTCAGGACTGAAGTGCTGT  
AAAGCAAGGAGCTGCTGAGAAGGAGCACTCCACTGTGTGCCTGGAGAATGGCTCTCACTA  
CTCACCTTGTCTTTTCTCAGCTTCCAGTGTCTTGGGTTTTTTTATACTTTGACAGCTTTTTTTT  
AATTGCATACATGAGACTGTGTTGACTTTTTTTTAGTTATGTGAAACACTTTGCCGCAGGC  
CGCCTGGCAGAGGCAGGAAATGCTCCAGCAGTGGCTCAGTGCTCCCTGGTGTCTGCTGCA  
TGGCATCCTGGATGCTTAGCATGCAAGTTCCTCCATCATTGCCACCTTGGTAGAGAGGG  
ATGGCTCCCCACCCTCAGCGTTGGGGATTACGCTCCAGCCTCCTTCTTGGTTGTCATAG  
TGATAGGGTAGCCTTATTGCCCCCTCTTCTTATACCCTAAAACCTTCTACACTAGTGCCA  
TGGGAACCAGGTCTGAAAAAGTAGAGAGAAGTGAAAGTAGAGTCTGGGAAGTAGCTGCCT  
ATAACTGAGACTAGACGGAAAAGGAATACTCGTGTATTTTAAGATATGAATGTGACTCAA  
GACTCGAGGCCGATACGAGGCTGTGATTCTGCCTTTGGATGGATGTTGCTGTACACAGAT  
GCTACAGACTTGTAACACACCGTAATTTGGCATTGTGTTAACCTCATTTATAAAAGC  
TTCAAAAAAACCCA

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**FIGURE 262**

MALRRPPRLRLCARLPDFFLLLLFRGCLIGAVNLKSSNRTPVVQEFESVELSCIITDSQT  
SDPRIEWKKIQDEQTTYVFFDNKIQGDLAGRAEILGKTS�KIWNVTRRDSALYRCEVVAR  
NDRKEIDEIVIELTVQVKPVPVCRVPKAVPVGKMATLHCQESEGHPRPHYSWYRNDVPL  
PTDSRANPRFRNSSFHLNSETGTLVFTAVHKDDSGQYYCIASNDAGSARCEEQEMEVDL  
NIGGIIGGVLVVLAVLALITLGICCAYYRRGYFINNKQDGESYKNPGKPDGVNYIRTDEEG  
DFRHKSSFVI

**Important features of the protein:**

**Signal peptide:**

amino acids 1-30

**Transmembrane domain:**

amino acids 243-263

**N-glycosylation sites:**

amino acids 104-107, 192-195

**cAMP- and cGMP-dependent protein kinase phosphorylation site:**

amino acids 107-110

**Casein kinase II phosphorylation site:**

amino acids 106-109, 296-299

**Tyrosine kinase phosphorylation site:**

amino acids 69-77

**N-myristoylation sites:**

amino acids 26-31, 215-220, 226-231, 243-248, 244-249, 262-267

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**FIGURE 263**

CCAGGACCAGGGCGCACCGGCTCAGCCTCTCACTTGTCTCAGAGGCCGGGGAAGAGAAGCAA  
AGCGCAACGGTGTGGTCCAAGCCGGGGCTTCTGCTTCGCCTCTAGGACATACACGGGACC  
CCCTAACTTCAGTCCCCCAAACGCGCACCCCTCGAAGTCTTGAACTCCAGCCCCGCACATC  
CACGCGCGGCACAGGCGCGGCAGGCGGCAGGTCCCGGCCGAAGGCGATGCGCGCAGGGGG  
TCGGGCAGCTGGGCTCGGGCGGCGGGAGTAGGGCCCGGCAGGGAGGCAGGGAGGCTGCAT  
ATTCAGAGTCGCGGGCTGCGCCCTGGGCAGAGGCCGCCCTCGCTCCACGCAACACCTGCT  
GCTGCCACCGCGCCGCGATGAGCCGCGTGGTCTCGCTGCTGCTGGGCGCGCGCTGCTCT  
GCGGCCACGGAGCCTTCTGCCGCCGCGTGGTCTCAGCGGCCAAAAGGTGTGTTTTGCTGACT  
TCAAGCATCCCTGCTACAAAATGGCCTACTTCCATGAACTGTCCAGCCGAGTGAGCTTTC  
AGGAGGCACGCTGGCTTGTGAGAGTGAGGGAGGAGTCTCTCCTCAGCCTTGAGAATGAAG  
CAGAACAGAAGTTAATAGAGAGCATGTTGCAAAACCTGACAAAACCCGGGACAGGGATTTC  
CTGATGGTGATTTCTGGATAGGGCTTTGGAGGAATGGAGATGGGCAAACATCTGGTGCCT  
GCCCAGATCTCTACAGTGGTCTGATGGAAGCAATTCCAGTACCGAACTGGTACACAG  
ATGAACCTTCTGCGGAAGTGAAAAGTGTGTTGTGATGTATCACCACCAACTGCCAATC  
CTGGCCTTGGGGGTCCCTACCTTTACAGTGGAAATGATGACAGGTGTAACATGAAGCACA  
ATTATATTTGCAAGTATGAACCAGAGATTAATCCAACAGCCCCTGTAGAAAAGCCTTATC  
TTACAAATCAACCAGGAGACACCCATCAGAATGTGGTTGTTACTGAAGCAGGTATAATTC  
CCAATCTAATTTATGTTGTTATACCAACAATACCCCTGCTCTTACTGATACTGGTTGCTT  
TTGGAACCTGTTGTTTCCAGATGCTGCATAAAAGTAAAGGAAGAACAACAACTAGTCCAA  
ACCAGTCTACACTGTGGATTTCAAAGAGTACCAGAAAAGAAAGTGGCATGGAAGTATAAT  
AACTCATTGACTTGGTTCCAGAATTTTGTAATTTCTGGATCTGTATAAGGAATGGCATCAG  
AACAATAGCTTGGAAATGGCTTGAAATCACAAAGGATCTGCAAGATGAACTGTAAGCTCCC  
CCTTGAGGCAAAATATTAAAGTAATTTTATATGTCTATTATTTTCAATTTAAAGAATATGCT  
GTGCTAATAATGGAGTGAGACATGCTTATTTTGCTAAAGGATGCACCCAACTTCAAAC  
TCAAGCAAATGAAATGGACAATGCAGATAAAGTTGTTATCAACACGTCGGGAGTATGTGT  
GTTAGAAGCAATTCCTTTTATTTCTTTCACCTTTCATAAGTTGTTATCTAGTCAATGTAA  
TGTATATTGTATTGAAATTTACAGTGTGCAAAAGTATTTTACCTTTGCATAAGTGTTTGA  
TAAAAATGAACTGTTCTAATATTTATTTTATGGCATCTCATTTTCAATACATGCTCTT  
TTGATTAAAGAACTTATTACTGTTGTCAACTGAATTCACACACACACAAATATAGTACC  
ATAGAAAAAGTTTGTCTCGAAATAATTCATCTTTCAGCTTCTCTGCTTTTGGTCAAT  
GTCTAGGAAATCTCTTCAGAAATAAGAAGCTATTTCAATTAAGTGTGATATAAACCTCCTC  
AAACATTTTACTTAGAGGCAAGGATTGTCTAATTTCAATTGTGCAAGACATGTGCCTTAT  
AATTATTTTACTTAAATTAACAGATTTTGTAATAATGTAACCTTGTGTAATAGGTGC  
ATAAACACTAATGCAGTCAATTTGAACAAAAGAAGTGACATACACAAATATAAATCATATG  
TCTTCACACGTTGCCTATATAATGAGAAGCAGCTCTCTGAGGGTTCTGAAATCAATGTGG  
TCCCTCTCTTGCCCACTAAACAAAGATGGTTGTTTCGGGGTTTGGGATTGACACTGGAGGC  
AGATAGTTGCAAAGTTAGTCTAAGGTTTCCCTAGCTGTATTTAGCCTCTGACTATATTAG  
TATACAAAGAGGTCATGTGGTTGAGACCAGGTGAATAGTCACTATCAGTGTGGAGACAAG  
CACAGCACACAGACATTTTAGGAAGGAAAGGAACTACGAAATCGTGTGAAAATGGGTTGG  
AACCCTCATGATCGCATATTCATTGATGAGGGTTTGCTTGAGATAGAAAATGGTGGCT  
CCTTTCTGTCTTATCTCCTAGTTTCTTCAATGCTTACGCCCTTGTTCTTCTCAAGAGAAAG  
TTGTAACCTCTCTGGTCTTCATATGTCCCTGTGCTCCTTTTAACCAATAAAGAGTTCTTG  
TTTCTGGGGGAA

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**FIGURE 264**

MSRVVSLLLGAALLCGHGAFRRVSVSGQKVCFADFKHPCYKMAYFHELSSRVSFQEARLA  
CESEGGVLLSLENEAEQKLIESMLQNLTKPGTGISDGD FWIGLWRNGDGQTS GACPDLYQ  
WSDGSNSQYRNWYTDEPSCGSEKCVVMYHQPTANPGLGGPYLYQWDDRCNMKHNYICKY  
EPEINPTAPVEKPYLTNQP GDTHQNVVVTEAGIIPNLIYVVIPTIPLLLLILVAFGTCCF  
QMLHKS KGRTKTSPNQSTLWISKSTRKESGMEV

**Important features of the protein:**

**Signal peptide:**

amino acids 1-21

**Transmembrane domain:**

amino acids 214-235

**N-glycosylation sites:**

amino acids 86-89 and 255-258

**cAMP- and cGMP-dependent protein kinase phosphorylation site:**

amino acids 266-269

**N-myristoylation sites:**

amino acids 27-32, 66-71, 91-96, 93-98, 102-107, 109-114, 140-145 and 212-217

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**FIGURE 265**

GGAGAATGGAGAGAGCAGTGAGAGTGGAGTCCGGGGTCCTGGTCCGGGTGGTCTGTCTGC  
TCCTGGCATGCCCTGCCACAGCCACTGGGCCCCGAAGTTGCTCAGCCTGAAGTAGACACCA  
CCCTGGGTCTGTGCGAGGCCGGCAGGTGGGCGTGAAGGGCACAGACCGCCTTGTGAATG  
TCTTTCTGGGCATTCCATTTGCCAGCCGCCACTGGGCCCCTGACCGTTCTCAGCCCCAC  
ACCCAGCACAGCCCTGGGAGGGTGTGCGGGATGCCAGCACTGCGCCCCCAATGTGCCTAC  
AAGACGTGGAGAGCATGAACAGCAGCAGATTGTCTCTCAACGGAAAACAGCAGATCTTCT  
CCGTTTCAGAGGACTGCCTGGTCTCAACGTCTATAGCCCAGCTGAGGTCCCCGCAGGGT  
CCGGTAGGCCGGTCATGGTATGGGTCCATGGAGGCGCTCTGATAACTGGCGCTGCCACCT  
CCTACGATGGATCAGCTCTGGCTGCCTATGGGGATGTGGTCTGTGGTTACAGTCCAGTACC  
GCCTTGGGGTCTTGGCTTCTTCAGCACTGGAGATGAGCATGCACCTGGCAACCAGGGCT  
TCCTAGATGTGGTAGCTGCTTTGCGCTGGGTGCAAGAAAACATCGCCCCCTTCGGGGGTG  
ACCTCAACTGTGTCACTGTCTTTGGTGGATCTGCCGGTGGGAGCATCATCTCTGGCCTGG  
TCCTGTCCCCAGTGGCTGCAGGGCTGTTCCACAGAGCCATCACACAGAGTGGGGTCATCA  
CCACCCAGGGATCATCGACTCTCACCTTGGCCCCCTAGCTCAGAAAATCGCAAACACCT  
TGGCCTGCAGCTCCAGCTCCCCGGCTGAGATGGTGCAGTGCCTTCAGCAGAAAGAAGGAG  
AAGAGCTGGTCTTAGCAAGAAGCTGAAAATACTATCTATCCTCTCACCGTTGATGGCA  
CTGTCTTCCCCAAAAGCCCCAAGGAACCTCTGAAGGAGAAGCCCTTCCACTCTGTGCCCT  
TCCTCATGGGTGTCAACAACCATGAGTTCAGCTGGCTCATCCCCAGGGGCTGGGGTCTCC  
TGGATACAATGGAGCAGATGAGCCGGGAGGACATGCTGGCCATCTCAACACCCGTCTTGA  
CCAGTCTGGATGTGCCCCCTGAGATGATGCCACCGTCATAGATGAATACCTAGGAAGCA  
ACTCGGACGCACAAGCCAAATGCCAGGCGTTCCAGGAATTCATGGGTGACGTATTCATCA  
ATGTTCCACCGTCAGTTTTTCAAGATACCTTCGAGATTCTGGAAGCCCTGTCTTTTTCT  
ATGAGTTCAGCATCGACCCAGTCTTTTTGCGAAGATCAAACCTGCCTGGGTGAAGGCTG  
ATCATGGGGCCGAGGGTGCTTTTGTGTTGCGAGGTCCCTTCCTCATGGACGAGAGCTCCC  
GCCTGGCCTTTCCAGAGGCCACAGAGGAGGAGAAGCAGCTAAGCCTCACCATGATGGCCC  
AGTGGACCCACTTTGCCCGGACAGGGGACCCCAATAGCAAGGCTCTGCCTCCTTGGCCCC  
AATTCAACCAGGCGGAACAATATCTGGAGATCAACCCAGTGCCACGGGCCGGACAGAAGT  
TCAGGGAGGCCTGGATGCAGTCTGGTTCAGAGACGCTCCCCAGCAAGATACAACAGTGGC  
ACCAGAAGCAGAAGAACAGGAAGGCCAGGAGGACCTCTGAGGGCCAGGCCTGAACCTTCT  
TGGCTGGGGCAAACCACTCTTCAAGTGGTGGCAGAGTCCCAGCACGGCAGCCCGCCTCTC  
CCCCTGCTGAGACTTTAATCTCCACCAGCCCTTAAAGTGTGCGCCGCTCTGTGACTGGAG  
TTATGCTCTTTTGAATGTCACAAGGCCGCTCCACCTCTGGGGCATTGTACAAGTTCT  
TCCCTCTCCCTGAAGTGCTTTTCTGCTTTCTTCGTGGTAGGTTCTAGCACATTCTCTA  
GCTTCCTGGAGGACTCACTCCCCAGGAAGCCTTCCCTGCCTTCTCTGGGCTGTGCGGCCC  
CGAGTCTGCGTCCATTAGAGCACAGTCCACCCGAGGCTAGCACCGTGTCTGTGTCTGTCT  
CCCCCTCAGAGGAGCTCTCTCAAAATGGGGATTAGCCTAACCCCACTCTGTCACCACAC  
CAGGATCGGGTGGGACCTGGAGCTAGGGGGTGTGTTGCTGAGTGAGTGAGTGAAACACAGA  
ATATGGGAATGGCAGCTGCTGAACCTGAACCCAGAGCCTTCAGGTGCCAAAGCCATACTC  
AGGCCCCCACCAGCATTTGTCCACCCTGGCCAGAAGGGTGCATGCCAATGGCAGAGACCTG  
GGATGGGAGAAGTCTGGGGCGCCAGGGGATCCAGCCTAGAGCAGACCTTAGCCCCCTGAC  
TAAGGCCCTCAGACTAGGGCGGGAGGGGTCTCCTCCTCTCTGCTGCCCAGTCTTGGCCCCCT  
GCACAAGACAACAGAATCCATCAGGGCCATGAGTGTCAACCAGACCTGACCCTCACCAAT  
TCCAGCCCCCTGACCCTCAGGACGCTGGATGCCAGCTCCCAGCCCCAGTGCCGGGTCTCC  
CTCCCTTCTGGCTTGGGGAGACCAGTTTCTGGGGAGCTTCCAAGAGCACCCACCAAGAC  
ACAGCAGGACAGGCCAGGGGAGGGCATCTGGACCAGGGCATCCGTGCGGCTATTGTCA  
GAGAAAAGAAGAGACCCACCCACTCGGGCTGCAAAAGGTGAAAAGCACCAAGAGTTTTTC

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AGATGGAAGTGAGAGGTGACAGTGTGCTGGCAGCCCTCACAGCCCTCGCTTGCTCTCCCT  
GCCGCCTCTGCCTGGGCTCCCACTTTGGCAGCACTTGAGGAGCCCTTCAACCCGCCGCTG  
CACTGTAGGAGCCCCCTTTCTGGGCTGGCCAAGGCCGGAGCCAGCTCCCTCAGCTTGCGGG  
GAGGTGCGGAGGGAGAGGGGCGGGCAGGAACCGGGGCTGCGCGCAGCGCTTGCGGGCCAG  
AGTGAGTTCGGGTGGGCGTGGGCTCGGCGGGGCCCCACTCAGAGCAGCTGGCCGGCCCC  
AGGCAGTGAGGGCCTTAGCACCTGGGCCAGCAGCTGCTGTGCTCGATTTCTCGCTGGGCC  
TTAGCTGCCTCCCCGCGGGGCAGGGCTCGGGACCTGCAGCCCTCCATGCCTGACCCTCCC  
CCCACCCCCCGTGGGCTCCTGTGCGGCCGGAGCCTCCCCAAGGAGCGCCGCCCTGCTC  
CACAGCGCCCAGTCCCATCGACCACCCAAGGGCTGAGGAGTGCGGGTGACAGCGCGGGA  
CTGGCAGGCAGCTCCACCTGCTGCCCCAGTGCTGGATCCACTGGGTGAAGCCAGCTGGGC  
TCCTGAGTCTGGTGGGGACTTGGAGAACCTTTATGTCTAGCTAAGGGATTGTAAATACAC  
CGATGGGCACTCTGTATCTAGCTCAAGTTTGTAAACACACCAATCAGCACCCCTGTGTCT  
AGCTCAGTGTTTGTGAATGCACCAATCCACACTCTGTATCTGGCTACTCTGGTGGGGACT  
TGGAGAACCTTTGTGTCCACACTCTGTATCTAGCTAATCTAGTGGGGATGTGGAGAACCT  
TTGTGTCTAGCTCAGGGATCGTAAACGCACCAATCAGCACCCCTGTCAAAACAGACCACTT  
GACTCTCTGTAAAATGGACCAATCAGCAGGATGTGGGTGGGGCGAGACAAGAGAATAAAA  
GCAGGCTGCCTGAGCCAGCAGTGACAACCCCCCTCGGGTCCCCTCCCACGCCGTGGAAGC  
TTTGTTCCTTCGCTCTTTGCAATAAATCTTGCTACTGCCCAAAA



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**FIGURE 266**

MERAVRVESGVLVGVVCLLLACPATATGPEVAQPEVDTTLGRVVRGRQVGVKGTDRLVNVF  
LGIPFAQPPLGPDREFSAPHPAQPWEGVRDASTAPPMCLQDVESMNSSRFVLNGKQQIFSV  
SEDCLVLNVYSPA EVPAGSGRPVMVWVHGGALITGAATSYDGSALAAYGDVVVVTVQYRL  
GVLGFFSTGDEHAPGNQGF LDVVAALRWVQENIAPFGGDLNCVTVFGGSAGGSIISGLVL  
SPVAAGLFHRAITQSGVITTPGIIDSHPWPLAQKIAN TLACSSSSPAEMVQCLQQKEGEE  
LVL SKKLKNTIYPLTVDGTVPFKSPKELLKEKPFHSVPFLMGVNNHEFSWLI PRGWGLLD  
TMEQMSREDMLAISTPVLTS LDVPPPEMMPTVIDEYLG SNSDAQAKCQAFQEFMGDVFINV  
PTVSFSRYLRDSGSPVFFYEFQHRPSSFAKIKPAWVKADHGAEGAFVFGGPFLMDESSRL  
AFPEATEEEKQLSLTMM AQWTHFARTGDPNSKALPPWPQFNQAEQYLEINPVPRAGQKFR  
EAWMQFWSETLP SKIQQWHQKQKNRKAQEDL

**Important features of the protein:**

**Signal peptide:**

amino acids 1-27

**Transmembrane domain:**

amino acids 226-245

**N-glycosylation site:**

amino acids 105-109

**N-myristoylation sites:**

amino acids 10-16, 49-55, 62-68, 86-92, 150-156, 155-161,  
162-168, 217-223, 227-233, 228-234, 232-238, 262-268, 357-363,  
461-467

**Prokaryotic membrane lipoprotein lipid attachment site:**

amino acids 12-23

**Carboxylesterases type-B serine active site:**

amino acids 216-232

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## FIGURE 267

TGTCGCCTGGCCCTCGCCATGCAGACCCCGCGAGCGTCCCCTCCCCGCCCGGCCCTCCTG  
CTTCTGCTGCTGCTACTGGGGGGCGCCACGGCCTCTTTCCTGAGGAGCCGCCGCCGCTT  
AGCGTGGCCCCCAGGGACTACCTGAACCACTATCCCGTGTTTGTGGGCAGCGGGCCCCGGA  
CGCCTGACCCCGCAGAAGGTGCTGACGACCTCAACATCCAGCGAGTCCTGCGGGTCAAC  
AGGACGCTGTTCAATTGGGGACAGGGACAACCTCTACCGCGTAGAGCTGGAGCCCCCAGC  
TCCACGGAGCTGCGGTACCAGAGGAAGCTGACCTGGAGATCTAACCCAGCGACATAAAC  
GTGTGTGCGATGAAGGGCAAACAGGAGGGCGAGTGTGAAACTTCGTAAAGGTGCTGCTC  
CTTCGGGACGAGTCCACGCTCTTTGTGTGCGGTTCCAACGCCTTCAACCCGGTGTGCGCC  
AACTACAGCATAGACACCCTGCAGCCCGTCGGAGACAACATCAGCGGTATGGCCCGCTGC  
CCGTACGACCCCAAGCAGCCAATGTTGCCCTCTTCTCTGACGGGATGCTCTTCACAGCT  
ACTGTTACCGACTTCTTAGCCATTGATGCTGTCTATCTACCGCAGCCTCGGGGACAGGCCC  
ACCCTGCGCACCCTGAAACATGACTCCAAGTGGTTCAAAGAGCCTTACTTTGTCCATGCG  
GTGGAGTGGGGCAGCCATGTCTACTTCTTCTTCGGGAGATTGCGATGGAGTTTAACTAC  
CTGGAGAAGGTGGTGGTGTCCCGCGTGGCCCGAGTGTGCAAGAACGACGTGGGAGGCTCC  
CCCCGCGTGCTGGAGAAGCAGTGGACGTCCTTCTGAAGGCGCGGCTCAACTGCTCTGTA  
CCCGGAGACTCCCATTCTACTTCAACGTGCTGCAGGCTGTACGGGCGTGGTTCAGCCTC  
GGGGGCCCGCCCGTGGTCTTGGCCGTTTTTTCCACGCCAGCAACAGCATCCCTGGCTCG  
GCTGTCTGCGCCTTTGACCTGACACAGGTGGCAGCTGTGTTTGAAGGCCGCTTCCGAGAG  
CAGAAGTCCCCGAGTCCATCTGGACGCCGGTGCCGGAGGATCAGGTGCCTCGACCCCGG  
CCCGGGTGCTGCGCAGCCCCCGGGATGCAGTACAATGCCTCCAGCGCCTTGCCGGATGAC  
ATCCTCAACTTTGTCAAGACCCACCCTCTGATGGACGAGGCGGTGCCCTCGCTGGGCCAT  
GCGCCCTGGATCCTGCGGACCCTGATGAGGCACCAGCTGACTCGAGTGGCTGTGGACGTG  
GGAGCCGGCCCCCTGGGGCAACCAGACCGTTGTCTTCTGAGGCGGGGACGGTTC  
CTCAAGTTCCTCGTCCGGCCCAATGCCAGCACCTCAGGGACGTCTGGGCTCAGTGTCTTC  
CTGGAGGAGTTTGAGACCTACCGGCCGGACAGGTGTGGACGGCCCGCGGTGGCGAGACA  
GGGCAGCGGCTGCTGAGCTTGAGCTGGACGCGAGCTTCGGGGGGCCTGCTGGCTGCCTTC  
CCCCGCTGCGTGGTCCGAGTGCCTGTGGCTCGCTGCCAGCAGTACTCGGGGTGTATGAAG  
AACTGTATCGGCAGTCAGGACCCCTACTGCGGGTGGGCCCCCGACGGCTCCTGCATCTTC  
CTCAGCCCCGGGCACCAGAGCCGCCCTTTGAGCAGGACGTGTCCGGGGCCAGCACCTCAGGC  
TTAGGGGACTGCACAGGACTCCTGCGGGCCAGCCTCTCCGAGGACCGCGCGGGGCTGGTG  
TCGGTGAACCTGCTGGTAACGTGCTCGGTGGCGGCCTTCGTGGTGGGAGCCGTGGTGTCC  
GGCTTCAGCGTGGGCTGGTTCGTGGGCCTCCGTGAGCGGCGGGAGCTGGCCCCGCGCAAG  
GACAAGGAGGCCATCCTGGCGCACGGGGCGGGCGAGGCGGTGCTGAGCGTCAGCCGCCTG  
GGCGAGCGCAGGGCGCAGGGTCCCGGGGGCGGGGCGGAGGCGGTGGCGGTGGCGCCGGG  
GTTCCCCCGGAGGCCCTGCTGGCGCCCTGATGCAGAACGGCTGGGCCAAGGCCACGCTG  
CTGCAGGGCGGGCCCCACGACCTGGACTCGGGGCTGCTGCCACGCCCGAGCAGACGCCG  
CTGCCGCAGAAGCGCCTGCCCACTCCGCACCCCGCACCCCCACGCCCTGGGCCCCCGCGCC  
TGGGACCACGGCCACCCCTGCTCCCGGCCTCCGCTTCATCCTCCCTCCTGCTGCTGGCG  
CCCCCCCCGGGCCCCCGAGCAGCCCCCGCGCCTGGGGAGCCGACCCCGACGGCCGCCTC  
TATGCTGCCCCGGCCCCGGCGCGCCTCCACGGCGACTTCCCGCTCACCCCCACGCCAGC  
CCGGACCGCCGGCGGGTGGTGTCCGCGCCACGGGCCCTTGGACCCAGCCTCAGCCGCC  
GATGGCCTCCCGCGGCCCTGGAGCCCGCCCCCGACGGGCAGCCTGAGGAGGCCACTGGGC  
CCCCACGCCCTCCGGCCGCCACCCTGCGCCGCACCCACACGTTCAACAGCGGCGAGGCC  
CGGCCTGGGGACCGCCACCGCGGTGCCACGCCCGGGCGGGCACAGACTTGGCCACCTC  
CTCCCCATATGGGGGGCGGACAGGACTGCGCCCCCGTGGCTTAGGCCGGGGGCCCCCG  
ATGCCCTTGGCAGTGCCAGCCACGGGAACCAGGAGCGAGAGACGGTGCCAGAACGCCGGGG  
CCCCGGGCAACTCCGAGTGGGTGCTCAAGTCCCCCGCGACCCACCCGCGGAGTGGGG

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GCCCCCTCCGCCACAAGGAAGCACAAACCAGCTCGCCCTCCCCCTACCCGGGGCCGCAGGA  
CGCTGAGACGGTTTGGGGGTGGGTGGGCGGGAGGACTTTGCTATGGATTTGAGGTTGACC  
TTATGCGCGTAGGTTTGGTTTGTTCAGTTTGGTTTCTTTTGGGTTTTCTAACC  
AATTGCACAACTCCGTTCTCGGGGTGGCGGCAGGCAGGGGAGGCTTGGACGCCGGTGGGG  
AATGGGGGGCCACAGCTGCAGACCTAAGCCCTCCCCACCCCTGGAAAGGTCCCTCCCCA  
ACCCAGGCCCCCTGGCGTGTGTGGGTGTGCGTGCGTGCGTGCGTGCGTGCGTGCGTGCAAGG  
GGCCGGGGAGGTGGGCGTGTGTGTGCGTGCCAGCGAAGGCTGCTGTGGGCGTGTGTGTCA  
AGTGGGCCACGCGTGCAGGGTGTGTGTCCACGAGCGACGATCGTGGTGGCCCCAGCGGCC  
TGGGCGTTGGCTGAGCCGACGCTGGGGCTTCCAGAAGGCCCGGGGGTCTCCGAGGTGCCG  
GTTAGGAGTTTGAACCCCCCCCCACTCTGCAGAGGGAAGCGGGGACAATGCCGGGGTTTCA  
GGCAGGAGACACGAGGAGGGCCTGCCCCGAAGTCACATCGGCAGCAGCTGTCTAAAGGGC  
TTGGGGGCCTGGGGGGCGGCGAAGGTGGGTGGGGCCCCCTCTGTAAATACGGCCCCAGGGT  
GGTGAGAGAGTCCCATGCCACCCGTCCCCTTGTGACCTCCCCCTATGACCTCCAGCTGA  
CCATGCATGCCACGTGGCTGGCTGGGTCTCTGCCCTCTTTGGAGTTTGCCTCCCCCAGC  
CCCCTCCCCATCAATAAACTCTGTTTACAACCAAAAAAAAAAAAAAAAAAAAAAAAAA

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**FIGURE 268**

MQTPRASPPRPALLLLLLLLGGAGHGLFPPEPPPLSVAPRDYLNHYPVFVGSGPGRLLTPAE  
GADDLNIQVRVLRVNRTLFIGDRDNLRYRVELEPPTSTELRYQRKLTWRSNPSDINVCRMKG  
KQEGECRNFKVLLLRDESTLFVCGSNAFNPVCANYSIDTLQPVGDNISGMARCPYDPKH  
ANVALFSDGMLFTATVTDFLAIDAVIYRSLGDRPTLRTVKHDSKWFKEPYFVHAVEWGS  
VYFFFREIAMEFNYLEKVVVSRVARVCKNDVGGSPRVLEKQWTSFLKARLNCSVPGDSHF  
YFNVLQAVTGVSLSGGRPVVLAVFSTPSNSIPGSAVCAFDLTQVAAVFEGRFREQKSPES  
IWTPVPEDQVPRPRPGCCAAPGMQYNASSALPDDILNFVKTHPLMDEAVPSLGHPWILR  
TLMRHQLTRVAVDVGAGPWGNQTVVFLGSEAGTVLKFLVRPNASTSGTSGLSVFLEEFET  
YRPDRCGRPGGGETGQRLLSLELDAASGGLLAAPRCVVRVPVARCQQYSGCMKNCIGSQ  
DPYCGWAPDGSCIFLSPGTRAAFEQDVSGASTSGLGDCGTGLLRASLSEDRAGLVSNNLLV  
TSSVAAFVVGAVVSGFSVGFVGLRERRELARRKDKEAILAHGAGEAVLSVSRLGERRAQ  
GPGGRGGGGGGGAGVPPEALLAPLMQNGWAKATLLQGGPHDLDSGLLPTPEQTPLPQKRL  
PTPHPHPHALGPRAWDHGHPLLPASASSLLLLAPARAPEQPPAPGEPTPDGRLYAARPG  
RASHGDFPLTPHASPDRRRVVSAPTGPLDPASAADGLPRPWSPPPTGSLRRPLGPHAPPA  
ATLRRTHTFNSGEARPGDRHRGCHARPGTDLAHLPLPYGGADRTAPPVP

**Important features of the protein:****Signal peptide:**

amino acids 1-25

**Transmembrane domains:**

amino acids 318-339, 598-617

**N-glycosylation sites.**amino acids 74-78, 155-159, 167-171, 291-295, 386-390,  
441-445, 462-466**Glycosaminoglycan attachment sites:**

amino acids 51-55, 573-577

**cAMP- and cGMP-dependent protein kinase phosphorylation site:**

amino acids 102-106

**N-myristoylation sites:**amino acids 21-27, 50-56, 189-195, 333-339, 382-388, 448-454,  
490-496, 491-497, 508-514, 509-515, 531-537, 558-564, 569-575,  
574-580, 580-586, 610-616, 643-649, 663-669, 666-672, 667-673,  
668-674, 669-675, 670-676, 868-874, 879-885

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**FIGURE 269**

ATCTGAGTGAGCTAACTGACACAATGAACTGTCAGGCATGTTTCTGCTCCTCTCTCTGG  
CTCTTTTCTGCTTTTAAACAGGTGTCTTCAGTCAGGGAGGACAGGTTGACTGTGGTGAGT  
TCCAGGACCCCAAGGTCTACTGCACTCGGGAATCTAACCACACTGTGGCTCTGATGGCC  
AGACATATGGCAATAAATGTGCCTTCTGTAAGGCCATAGTGAAAAGTGGTGAAAGATTA  
GCCTAAAGCATCCTGGAAAATGCTGAGTTAAAGCCAATGTTTCTTGGTGACTTGCCAGCT  
TTTGCAGCCTTCTTTTCTCACTTCTGCTTATACTTTTGCTGGTGGATTCTTTAATTCAT  
AAAGACATACCTACTCTGCCTGGGTCTTGAGGAGTTCAATGTATGTCTATTTCTCTTGAT  
TCACTTGTCAATAAAGTACATTCTGCAAAAGCAAAA

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## FIGURE 270

MKLSGMFLLLSLALFCFLTGVFSQGGQVDCGEFQDPKVYCTRESNPFCGSDGQTYGNKCA  
FCKAIVKSGGKISLKHPGKC

**Important features of the protein:**

**Signal peptide:**

amino acids 1-23

**N-myristoylation sites:**

amino acids 26-32, 52-58, 56-62, 69-75

**Kazal serine protease inhibitors family signature:**

amino acids 40-63

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**FIGURE 271**

AACTTCTACATGGGCCTCCTGCTGCTGGTGCTCTTCCTCAGCCTCCTGCCGGTGGCCTAC  
ACCATCATGTCCCTCCCACCCTCCTTTGACTGCGGGCCGTTCAGGTGCAGAGTCTCAGTT  
GCCCCGGGAGCACCTCCCCTCCCGAGGCAGTCTGCTCAGAGGGCCTCGGCCCAGAATTCCA  
GTTCTGGTTTCATGCCAGCCTGTAAAAGGCCATGGAACTTTGGGTGAATCACCGATGCCA  
TTTAAGAGGGTTTTCTGCCAGGATGGAAATGTTAGGTCGTTCTGTGTCTGCGCTGTTTCAT  
TTCAGTAGCCACCAGCCACCTGTGGCCGTTGAGTGCTTGAAATGAGGAACTGAGAAAATT  
AATTTCTCATGTATTTTTCTCATTTATTTATTAATTTTTAACTGATAGTTGTACATATTT  
GGGGGTACATGTGATATTTGGATACATGTATACAATATATAATGATCAAATCAGGGTAAC  
TGGGATATCCATCACATCAAACATTTATTTTTTATTCTTTTTTAGACAGAGTCTCACTCTG  
TCACCCAGGCTGGAGTGCAGTGGTGCCATCTCAGCTTACTGCAACCTCTGCCTGCCAGGT  
TCAAGCGATTCTCATGCCTCCACCTCCCAAGTAGCTGGGACTACAGGCATGCACCACAAT  
GCCCAACTAATTTTTGTATTTTTAGTAGAGACGGGGTTTTGCCATGTTGCCCAGGCTGGC  
CTTGAACCTCCTGGCCTCAAACAATCCACTTGCCTCGGCCTCCCAAAGTGTTATGATTACA  
GGCGTGAGCCACCGTGCCTGGCCTAAACATTTATCTTTTCTTTGTGTTGGGAACTTTGAA  
ATTATACAATGAATTATTGTAACTGTCATCTCCCTGCTGTGCTATGGAACACTGGGACT  
TCTTCCCTCTATCTAACTGTATATTTGTACCAGTTAACCAACCGTACTTCATCCCCACTC  
CTCTCTATCCTTCCCAACCTCTGATCACCTCATTTCTACTCTCTACCTCCATGAGATCCAC  
TTTTTTAGCTCCCACATGTGAGTAAGAAAATGCAATATTTGTCTTTCTGTGCCTGGCTTA  
TTTCACTTAACATAATGACTTCCTGTTCCATCCATGTTGCTGCAAATGACAGGATTTTCGT  
TCTTAATTTCAATTAAAATAACCAACATGGCAAAAA

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## FIGURE 272

MGLLLLVLFLSLLPVAYTIMSLPPSFDCGPFRCRVSVAREHLPSRGSLLRGPRPRI PVLV  
SCQPVKGHGTLGESPMPPFKRVFCQDGNVRSFCVCAVHFSSHQPPVAVECLK

**Important features of the protein:**

**Signal peptide:**

amino acids 1-18

**N-myristoylation site:**

amino acids 86-92

**Zinc carboxypeptidases, zinc-binding region 2 signature:**

amino acids 68-79



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**FIGURE 273**

TTCTGAAGTAACGGAAGCTACCTTGTATAAAGACCTCAACACTGCTGACCATGATCAGCG  
CAGCCTGGAGCATCTTCCTCATCGGGACTAAAATTGGGCTGTTCTTCAAGTAGCACCTC  
TATCAGTTATGGCTAAATCCTGTCCATCTGTGTGTGCTGCGATGCGGGTTTCATTTACT  
GTAATGATCGCTTTCTGACATCCATTCCAACAGGAATACCAGAGGATGCTACAACCTCTCT  
ACCTTCAGAACAAACCAAATAAATAATGCTGGGATTCTTTCAGATTTGAAAACTTGCTGA  
AAGTAGAAAGAATATACCTATACCACAACAGTTTAGATGAATTTCTTACCAACCTCCCAA  
AGTATGTAAAAGAGTTACATTTGCAAGAAAATAACATAAGGACTATCACTTATGATTAC  
TTTCAAAAATTCCCTATCTGGAAGAATTACATTTAGATGACAACTCTGTCTCTGCAGTTA  
GCATAGAAGAGGGAGCATTCGAGACAGCAACTATCTCCGACTGCTTTTCTGTCCCCTA  
ATCACCTTAGCACAAATCCCTGGGGTTTGCCAGGACTATAGAAGAACTACGCTTGGATG  
ATAATCGCATATCCACTATTTTCATCACCATCTCTTCAAGGTCTCACTAGTCTAAAACGCC  
TGGTCTTAGATGGAAACCTGTTGAACAATCATGGTTTAGGTGACAAAGTTTCTTCAACC  
TAGTTAATTTGACAGAGCTGTCCCTGGTGCGGAATCCCTGACTGCTGCACCAGTAAACC  
TTCCAGGCACAAACCTGAGGAAGCTTTATCTTCAAGATAACCACATCAATCGGGTGCCCC  
CAAATGCTTTTCTTATCTAAGGCAGCTCTATCGACTGGATATGTCCAATAATAACCTAA  
GTAATTTACCTCAGGGTATCTTTGATGATTTGGACAATATAACACAACCTGATTCTTCGCA  
ACAATCCCTGGTATTGCGGGTGCAAGATGAAATGGGTACGTGACTGGTTACAATCACTAC  
CTGTGAAGGTCAACGTGCGTGGGCTCATGTGCCAAGCCCCAGAAAAGGTTCTGTTGGATGG  
CTATTAAGGATCTCAATGCAGAACTGTTTGATTGTAAGGACAGTGGGATTGTAAGCACCA  
TTCAGATAACCACTGCAATACCCAACACAGTGTATCCTGCCCCAAGGACAGTGGCCAGCTC  
CAGTGACCAAAACAGCCAGATATTAAGAACCCCAAGCTCACTAAGGATCAACAAACCACAG  
GGAGTCCCTCAAGAAAAACAATTACAATTACTGTGAAGTCTGTACCTCTGATACCATTCT  
ATATCTCTTGAAACTTGCTCTACCTATGACTGCTTTGAGACTCAGCTGGCTTAAACTGG  
GCCATAGCCCCGGCATTGTTGATCTATAACAGAAACAATTGTAACAGGGGAACGCAGTGAGT  
ACTTGGTCACAGCCCTGGAGCCTGATTCACCCCTATAAAGTATGCATGGTTCCCATGGAAA  
CCAGCAACCTCTACCTATTTGATGAAACTCCTGTTTGTATTGAGACTGAAACTGCACCCC  
TTCGAATGTACAACCCTACAACCACCCTCAATCGAGAGCAAGAGAAAGAACCTTACAAAA  
ACCCCAATTTACCTTTGGCTGCCATCATTGGTGGGGCTGTGGCCCTGGTTACCATTGCCC  
TTCTTGCTTTAGTGTGTTGGTATGTTTCATAGGAATGGATCGCTCTTCTCAAGGAACGTGTG  
CATATAGCAAAGGGAGGAGAAGAAAGGATGACTATGCAGAAGCTGGCACTAAGAAGGACA  
ACTCTATCCTGGAAATCAGGGAAACTTCTTTTCAGATGTTACCAATAAGCAATGAACCCA  
TCTCGAAGGAGGAGTTTGTAAACACACCATATTTCTCCTAATGGAATGAATCTGTACA  
AAAACAATCACAGTGAAAGCAGTAGTAACCGAAGCTACAGAGACAGTGGTATTCCAGACT  
CAGATCACTCACACTCATGATGCTGAAGGACTCACAGCAGACTTGTGTTTTGGGTTTTTT  
AAACCTAAGGGAGGTGATGGT

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**FIGURE 274**

MISAAWSIFLIGTKIGLFLQVAPLSVMAKSCPSVCRCDAGFIYCNDRFLTSIPTGIPEDA  
TTLYLQNNQINNAGIPSDLKNLLKVERIYLYHNSLDEFPTNLPKYVKELHLQENNIRTIT  
YDSLSKIPYLEELHLDDNSVSAVSIIEGAFRDSNYLRLLFLSRNHLSTIPWGLPRTIEEL  
RLDDNRISTISSPSLQGLTSLKRLVLDGNLLNNHGLGDKVFFNLVNLTELSLVRNSLTAA  
PVNLPGTNLRKLYLQDNHINRVPPNAFSYLRQLYRLDMSNNNLSNLPQGI FDDLDNITQL  
ILRNNPWYCGCKMKWVRDWLQSLPVKVNVRGLMCQAPEKVRGMAIKDLNAELFDCKDSGI  
VSTIQITTAIPNTVYPAQGQWPAPVTKQPDIKNPKLTKDQQTGSPSRKTITITVKSPTS  
DTIHISWKLALPMTALRLSWLKLGHSPAFGSITETIVTGERSEYLVTALEPDSPYKVMV  
PMETSNLYLFDETPVCIEETETAPLRMYNPTTTLNREQEKEPYKNPNLPLAAIIGGAVALV  
TIALALLVCWYVHRNGSLFSRNCAYSKGRRRKDDYAEAGTKKDNSILEIRETSFQMLPIS  
NEPISKEEFVIHTIFPPNGMNLYKNNHSESSSNRSYRDSGIPDSHSHS

**Important features of the protein:****Signal peptide:**

amino acids 1-28

**Transmembrane domain:**

amino acids 531-552

**N-glycosylation sites:**

amino acids 226-229, 282-285, 296-299, 555-558, 626-629, 633-636

**Tyrosine kinase phosphorylation site:**

amino acids 515-522

**N-myristoylation sites:**

amino acids 12-17, 172-177, 208-213, 359-364, 534-539, 556-561, 640-645

**Amidation site:**

amino acids 567-570

**Leucine zipper pattern:**

amino acids 159-180

**Phospholipase A2 aspartic acid active site:**

amino acids 34-44

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**FIGURE 275.**

AGGGCCCGGGGTGGAGAGAGCGACGCCCCGAGGGGATGGCGGCAGCGTCCCCGAGCGCCT  
CTGGCTGGGCGCTACTGCTGCTGGTGGCACTTTGGCAGCAGCGCGCGGCGGCTCCGGCG  
TCTTCCAGCTGCAGCTGCAGGAGTTCATCAACGAGCGCGGCGTACTGGCCAGTGGGCGGC  
CTTGCAGAGCCCGGCTGCCGGAATTTCTTCCGCGTCTGCCCTTAAGCACTTCCAGGCGGTCTG  
TCTCGCCCCGACCTTGCACCTTCGGGACCGTCTCCACGCCGGTATTGGGCACCAACTCCT  
TCGCTGTCCGGGACGACAGTAGCGGCGGGGGCGCAACCCTCTCCAAGTGCCTTCAATT  
TCACCTGGCCGGGTACCTTCTCGCTCATCATCGAAGCTTGGCACGCGCCAGGAGACGACC  
TGCGGCCAGAGGCGCTTGCCACCAGATGCACTCATCAGCAAGATCGCCATCCAGGGCTCCC  
TAGCTGTGGGTGAGAACTGGTTATTGGATGAGCAAACCAGCACCTCACAAGGCTGCGCT  
ACTCTTACCGGCTCATCTGCAGTGACAACTACTATGGAGACAACTGCTCCCGCTGTGCA  
AGAAGCGCAATGACCACTTCGGCCACTATGTGTGCCAGCCAGATGGCAACTTGTCTGTCC  
TGCCCGGTTGGACTGGGGAATATTGCCAACAGCCTATCTGTCTTTCGGGCTGTGATGAAC  
AGAATGGCTACTGCAGCAAGCCAGCAGAGTGCCCTCTGCCGCCAGGCTGGCAGGGCCGGC  
TGTGTAACGAATGCATCCCCACAATGGCTGTGCCACGGCACCTGCAGCACTCCCTGGC  
AATGTACTTGTGATGAGGGCTGGGGAGGCGCTGTTTTGTGACCAAGATCTCAACTACTGCA  
CCCACCACTCCCATGCAAGAATGGGGCAACGTGCTCCAACAGTGGGCAGCGAAGCTACA  
CCTGCACCTGTGCCCCAGGCTACACTGGTGTGGACTGTGAGCTGGAGCTCAGCGAGTGTG  
ACAGCAACCCCTGTGCAATGGAGGCAGCTGTAAGGACCAGGAGGATGGCTACCACTGCC  
TGTGTCTTCCGGGCTACTATGGCCTGCACTGTGAACACAGCACCTTGAGCTGCGCCGACT  
CCCCCTGCTTCAATGGGGGCTCCTGCCGGGAGCGCAACCAGGGGGGCAACTATGCTTGTG  
AATGTCCCCCAACTTCACCGGCTCCAAGTGCAGAGAAAGTGGACAGGTGCACCAGCA  
ACCCCTGTGCCAACGGGGGACAGTGCCCTGAACCGAGGTCCAAGCCGCATGTGCCGCTGCC  
GTCCTGGATTACAGGGCACCTACTGTGAAGTCCACGTGAGCGACTGTGCCCGTAACCTT  
GCGCCACGGTGGCACTTGCCATGACCTGGAGAATGGGCTCATGTGCACCTGCCCTGCCG  
GCTTCTCTGGCCGACGCTGTGAGGTGCGGACATCCATCGATGCCTGTGCCCTCGAGTCCCT  
GCTTCAACAGGGCCACCTGCTACACCGACCTCTCCACAGACACCTTTGTGTGCAACTGCC  
CTTATGGCTTTGTGGGCAGCCGCTGCGAGTTCCCCGTGGGCTTGCCGCCAGCTTCCCCCT  
GGGTGGCCGTCTCGCTGGGTGTGGGGCTGGCAGTGCTGCTGGTACTGCTGGGCATGGTGG  
CAGTGGCTGTGCGGCAGCTGCGGCTTCGACGGCCGGACGACGGCAGCAGGGAAGCCATGA  
ACAACTTGTGCGACTTCCAGAAGGACAACCTGATTCTGCGGCCAGCTTAAAAACACAA  
ACCAGAAGAAGGAGCTGGAAGTGGACTGTGGCCTGGACAAGTCCAAGTGTGGCAAACAGC  
AAAACACACATTGGACTATAATCTGGCCCCAGGGCCCCCTGGGGCGGGGACCATGCCAG  
GAAAGTTTCCCACAGTGACAAGAGCTTAGGAGAGAAGGCGCCACTGCGGTTACACAGTG  
AAAAGCCAGAGTGTGCGATATCAGCGATATGCTCCCCCAGGGACTCCATGTACCAGTCTG  
TGTGTTTGATATCAGAGGAGAGGAATGAATGTGTGATTGCCACGGAGGTATAAGGCAGGA  
GCCTACCTGGACATCCCTGCTCAGCCCCGCGGCTGGACCTTCCTTCTGCATTGTTTACA

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**FIGURE 276**

MAAASRSASGWALLLLVALWQQRAAGSGVFQLQLQEFINERGVLASGRPCEPGCRTFFRV  
CLKHFQAVVSPGPCTFGTVSTPVLGTNSFAVRDDSSGGGRNPLQLPFNFTWPGTFSLIIE  
AWHAPGDDLRPEALPPDALISKIAIQGSLAVGQNWLLDEQTSTLTRLRYSYRVICSDNYY  
GDNC SRLCKKRNDHFGHYVCQPDGNLSCLPGWTGEYCQQPICLSGCHEQNGYCSKPAECL  
CRPGWQGRLCNECIPHNGCRHGTCSTPWQCTCDEGWGGLFCDQDLNYCTHHSPCKNGATC  
SNSGQRSYTCCTCRPGYTGVDCELELSECDSNPCRNGGSKDQEDGYHCLCPPGYGLHCE  
HSTLSCADSPCFNGGSCRERNQGANYACECPPNFTGNSCEKKVDRCTSNPCANGGQCLNR  
GPSRMCRCRPGFTGTYCELHVSDCARNPCAAGGTCHDLENGLMCTCPAGFSGRRCEVRTS  
IDACASSPCFN RATCYTDLSTDTFVCNCPYGFVGSRCFFVGLPPSFPWVAVSLGVGLAV  
LLVLLGMVAVAVRQLRLRRPDGDSREAMNNLSDFQKDNLI PAAQLKNTNQKKELEVDCGL  
DKSNCGKQQNHTLDYNLAPGPLGRGTMFGKFPHSDKSLGEKAPLRLHSEKPECRISAICS  
PRDSMYQSVCLISEERNECVIATEV

**Important features of the protein:**

**Signal peptide:**

amino acids 1-26

**Transmembrane domain:**

amino acids 530-552

**N-glycosylation sites:**

amino acids 108-112, 183-187, 205-209, 393-397, 570-574,  
610-614

**Glycosaminoglycan attachment site:**

amino acids 96-100

**Tyrosine kinase phosphorylation site:**

amino acids 340-347

**N-myristoylation sites:**

amino acids 42-48, 204-210, 258-264, 277-283, 297-303,  
383-389, 415-421, 461-467, 522-528, 535-541, 563-569,  
599-605, 625-631

**Amidation site:**

amino acids 471-475

**Aspartic acid and asparagine hydroxylation site:**

amino acids 339-351

**EGF-like domain cysteine pattern signature:**

amino acids 173-185, 206-218, 239-251, 270-282, 310-322,  
348-360, 388-400, 426-438, 464-476, 506-518

**Calcium-binding EGF-like:**

amino acids 224-245, 255-276, 295-316, 333-354, 373-394,  
411-432, 449-470

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**FIGURE 277**

GGCAGTGCAGCCGCTCACAGGTCGGCGGACGGGCCAGGCGGGCGGCCTCCTGAACCGAA  
CCGAATCGGCTCCTCGGGCCGTGTCCTCCCGCCCCTCCTCGCCCGCCCGGAGTTTTC  
TTTCGGTTTCTTCCAAGATTCTGTCCTTCCCTCGACGGAGCCGGGCCAGTGCGGGGGC  
GCAGGGCGCGGAGCTCCACCTCCTCGGCTTTCCCTGCGTCCAGAGGCTGGCATGGCGCG  
GGCCGAGTACTGAGCGCACGGTCGGGGCACAGCAGGGCCGGGGGGTGCAGCTGGCTCGCG  
CCTCCTCTCCGGCCGCGTCTCCTCCGGTCCCTGGCGAAAGCCATTGAGACACCAGCTGG  
ACGTCACGCGCCGGAGCATGTCTGGGAGTCAGAGCGAGGTGGCTCCATCCCCGCAGAGTC  
CGCGGAGCCCCGAGATGGGACGGGACTTGCGGCCCGGGTCCCGCGTGCTCCTGCTCCTGC  
TTCTGCTCCTGCTGGTGTACCTGACTCAGCCAGGCAATGGCAACGAGGGCAGCGTCACTG  
GAAGTTGTTATTGTGGTAAAAGAATTTCTTCCGACTCCCCGCCATCGGTTCACTTCATGA  
ATCGTCTCCGAAACACCTGAGAGCTTACCATCGGTGTCTATACTACACGAGGTTCCAGC  
TCCTTTCTGAGCGTGTGTGGGGCAACAAGACCCATGGGTTTCAAGGAATTGATGAGCT  
GTCTTGATCTCAAAGAATGTGGACATGCTTACTCGGGGATTGTGGCCCACCAGAAGCATTT  
TACTTCCTACCAGCCCCCAATTTCTCAGGCCTCAGAGGGGGCATCTTCAGATATCCACA  
CCCCTGCCCAGATGCTCCTGTCCACCTTGCAGTCCACTCAGCGCCCCACCCTCCCAGTAG  
GATCACTGTCTCGGACAAAGAGCTCACTCGTCCCAATGAAACCACCATTACACTGCGG  
GCCACAGTCTGGCAGCTGGGCCTGAGGCTGGGGAGAACCAAGCAGCCGGAAAAAATG  
CTGGTCCCACAGCCAGGACATCAGCCACAGTGCCAGTCCTGTGCCTCCTGGCCATCATCT  
TCATCCTCACCAGCCCTTTCTATGTGCTGTGCAAGAGGAGGAGGGGGCAGTCACCGC  
AGTCCTCTCCAGATCTGCCGGTTCATTATATACCTGTGGCACCTGACTCTAATACCTGAG  
CCAAGAATGGAAGCTTGTGAGGGTAACTGTGGCTTATTCTTACAAAAAGTGAATAAAG  
GAGACTGACCCCTGACAACATGGTAGGCACTGTAAAAA

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**FIGURE 278**

MGRDLRPGSRVLLLLLLLLLLVYLTQPGNGNEGSVTGSCYCGKRISSDSPPSVQFMNRLRK  
HLRAYHRCCLYYTRFQLLSWSVCGGNKDPWVQELMSCLDLKECGHAYSGIVAHQKHLLPTS  
PPISQASEGASSDIHTPAQMLLSTLQSTQRPTLPVGSLSDDKELTRPNETTIHTAGHSLA  
AGPEAGENQKQPEKNAGPTARTSATVPVLCLLAIIFILTAALSYVLCKRRRGQSPQSSPD  
LPVHYIPVAPDSNT

**Important features of the protein:**

**Signal peptide:**

1-26

**Transmembrane domain:**

204-223

**N-glycosylation site:**

168-172

**cAMP- and cGMP-dependent protein kinase phosphorylation site:**

42-46

**N-myristoylation site:**

29-35, 32-38, 36-42, 156-162

**Amidation site:**

40-44



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**FIGURE 280**

MALLLCFVLLCGVVDFAFARSLSITTPPEEMIEKAKGETAYLPCKFTLSPEDQGPLDIEWLIS  
PADNQKVDQVIILYSGDKIYDDYYPDLKGRVHFTSNDLKSGDASINVTNLQLSDIGTYQC  
KVKKAPGVANKKIHLVVLVKPSGARCIVDGSSEEIGSDFKIKCEPKESLPLQYEWQKLS  
SQKMPTSWLAEMTSSVISVKNASSEYSGTYSCTVRNRVGSQCLLRNLNVPPSNKAGLIA  
GAIIGTLLALALIGLIIFCCRKKRREEKYEKEVHHDIREDVPPPKSRTSTARSYIGSNHS  
SLGSMSPSNMEGYSKTQYNQVPSEDFERTPQSPTLPPAKFKYPYKTDGITVV

**Signal sequence.**  
amino acids 1-19

**Transmembrane domain:**  
amino acids 236-257

**N-glycosylation sites:**  
amino acids 106-110, 201-205, 298-302

**Tyrosine kinase phosphorylation sites:**  
amino acids 31-39, 78-85, 262-270

**N-myristoylation sites:**  
amino acids 116-122, 208-214, 219-225, 237-243, 241-247,  
245-251, 296-302

**Myelin P0 protein:**  
amino acids 96-125



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**FIGURE 281**

TGCATCAGTGCCCAGGCAAGCCCAGGAGTTGACATTTCTCTGCCCAGCCATGGGCCTCAC  
CCTGCTCTTGCTGCTGCTCCTGGGACTAGAAGGTCAGGGCATAGTTGGCAGCCTCCCTGA  
GGTGCTGCAGGCACCCGTGGGAAGCTCCATTCTGGTGCAGTGCCACTACAGGCTCCAGGA  
TGTCAAAGCTCAGAAGGTGTGGTGCCGGTTCTTGCCGGAGGGGTGCCAGCCCCTGGTGTC  
CTCAGCTGTGGATCGCAGAGCTCCAGCGGGCAGGCGTACGTTTCTCACAGACCTGGGTGG  
GGGCCTGCTGCAGGTGGAATGGTTACCCTGCAGGAAGAGGATGCTGGCGAGTATGGCTG  
CATGGTGGATGGGGCCAGGGGGCCCCAGATTTTGCACAGAGTCTCTCTGAACATACTGCC  
CCCAGAGGAAGAAGAAGAGACCCATAAGATTGGCAGTCTGGCTGAGAACGCATTCTCAGA  
CCCTGCAGGCAGTGCCAACCCTTTGGAACCCAGCCAGGATGAGAAGAGCATCCCCCTTGAT  
CTGGGGTGCTGTGCTCCTGGTAGGTCTGCTGGTGGCAGCGGTGGTGCTGTTTGCTGTGAT  
GGCCAAGAGGAAACAAGAATCCCTCCTCAGTGGTCCACCACGTCACTGACTCTGGACCGG  
CTGCTGAATTGCCTTTGGATGTACCACACATTAGGCTTGACTCACCACCTTCATTTGACA  
ATACCACCTACACCAGCCTACCTCTTGATTCCCCATCAGGAAAACCTTCACTCCCAGCTC  
CATCCTCATTGCCCCCTCTACCTCCTAAGGTCCTGGTCTGCTCCAAGCCTGTGACATATG  
CCACAGTAATCTTCCCGGGAGGGAACAAGGGTGGAGGGACCTCGTGTGGGCCAGCCCAGA  
ATCCACCTAACAATCAGACTCCATCCAGCTAAGCTGCTCATCACACTTTAAACTCATGAG  
GACCATCCCTAGGGGTTCTGTGCATCCATCCAGCCAGCTCATGCCCTAGGATCCTTAGGA  
TATCTGAGCAACCAGGGACTTTAAGATCTAATCCAATGTCCTAACTTTACTAGGGAAAGT  
GACGCTCAGACATGACTGAGATGTCTTGGGGAAGACCTCCCTGCACCCAACTCCCCACT  
GGTTCTTCTACCATTACACACTGGGCTAAATAAACCTAATAATGATGTGCAAAAAAAAAA  
AA

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**FIGURE 282**

MGLTLLLLLLLLGLEGQGIVGSLPEVLQAPVGSSILVQCHYRLQDVKAQKVWCRFLPEGCO  
PLVSSAVDRRAPAGRRTFLTDLGCGLLQVEMVTLQEEDAGEYGCMDGARGPQILHRVSL  
NILPPEEEEEETHKIGSLAENAFSDPAGSANPLEPSQDEKSIPLIWGAVLLVGLLVAAVVL  
FAVMAKRKQESLLSGPPRQ

**Important features of the protein:****Signal peptide:**

amino acids 1-15

**Transmembrane domain:**

amino acids 161-181

**N-myristoylation sites:**

amino acids 17-23, 172-178

**Amidation site:**

amino acids 73-79

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**FIGURE 283**

GTAGCATAGTGTGCAGTTCCTGACCAAAAGCTTTGGCTGCACCTCTTCTGGAAAGCTG  
GCCATGGGGCTCTTCATGATCATTGCAATTCTGCTGTTCCAGAAACCCACAGTAACCGAA  
CAACTTAAGAAGTGCTGGAATAACTATGTACAAGGACATTGCAGGAAAATCTGCAGAGTA  
AATGAAGTGCCTGAGGCACTATGTGAAAATGGGAGATACTGTTGCCTCAATATCAAGGAA  
CTGGAAGCATGTAAAAAAATTACAAAGCCACCTCGTCCAAGCCAGCAACACTTGCACTG  
ACTCTTCAAGACTATGTTACAATAATAGAAAATTTCCCAAGCCTGAAGACACAGTCTACA  
TAAATCAAATACAATTTTCGTTTTCACTTGCTTCTCAACCTAGTCTAATAAACTAAGGTGA  
TGAGATATACATCTTCTTCCTTCTGGTTTCTTGATCCTTAAATGACCTTCGAGCATATT  
CTAATAAAGTGCATTGCCAGTTAAAAA

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## FIGURE 284

MGLFMIIAILLFQKPTVTEQLKKCWNNYVQGHCRKICRVNEVPEALCENGRYCCLNIKEL  
EACKKITKPPRPKPATLALTLDYVTIIENFPSLKTQST

Important features of the protein:

Signal peptide:

None

Transmembrane domain:

None

cAMP- and cGMP-dependent protein kinase phosphorylation site:

64-68

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**FIGURE 285**

GATGGCGCAGCCACAGCTTCTGTGAGATTTCGATTTCTCCCCAGTTCCCCTGTGGGTCTGA  
GGGGACCAGAAGGGTGAGCTACGTTGGCTTTCTGGAAGGGGAGGCTATATGCGTCAATTC  
CCCAAAACAAGTTTTGACATTTCCCCTGAAATGTCATTCTCTATCTATTCACTGCAAGTG  
CCTGCTGTTCCAGGCCTTACCTGCTGGGCACTAACGGCGGAGCCAGGATGGGGACAGAAT  
AAAGGAGCCACGACCTGTGCCACCAACTCGCACTCAGACTCTGAACTCAGACCTGAAATC  
TTCTCTTCACGGGAGGCTTGGCAGTTTTTCTTACTCCTGTGGTCTCCAGATTTTCAGGCCT  
AAGATGAAAGCCTCTAGTCTTGCCCTTCAGCCTTCTCTCTGCTGCGTTTTATCTCCTATGG  
ACTCCTTCCACTGGACTGAAGACACTCAATTTGGGAAGCTGTGTGATCGCCACAAACCTT  
CAGGAAATACGAAATGGATTTTTCTGAGATACGGGGCAGTGTGCAAGCCAAAGATGGAAAC  
ATTGACATCAGAATCTTAAGGAGGACTGAGTCTTTGCAAGACACAAAGCCTGCGAATCGA  
TGCTGCCTCCTGCGCCATTTGCTAAGACTCTATCTGGACAGGGTATTTAAAACTACCAG  
ACCCCTGACCATTATACTCTCCGGAAGATCAGCAGCCTCGCCAATTCCTTTCTTACCATC  
AAGAAGGACCTCCGGCTCTCTCATGCCCACATGACATGCCATTGTGGGGAGGAAGCAATG  
AAGAAATACAGCCAGATTCTGAGTCACTTTGAAAAGCTGGAACCTCAGGCAGCAGTTGTG  
AAGGCTTTGGGGGAAGTAGACATTCTTCTGCAATGGATGGAGGAGACAGAAATAGGAGGAA  
AGTGATGCTGCTGCTAAGAATATTCGAGGTCAGAGCTCCAGTCTTCAATACCTGCAGAG  
GAGGCATGACCCCAAACCACCATCTCTTTACTGTACTAGTCTTGTGCTGGTCACAGTGTA  
TCTTATTTATGCATTACTTGCTTCCTTGCATGATTGTCTTTATGCATCCCCAATCTTAAT  
TGAGACCATACTTGTATAAGATTTTTGTAAATATCTTTCTGCTATTGGATATATTTATTAG  
TTAATATATTTATTTATTTTTTGCTATTTAATGTATTTATTTTTTTACTTTGGACATGAAA  
CTTTAAAAAAATTCACAGATTATATTTATAACCTGACTAGAGCAGGTGATGTATTTTTAT  
ACAGTAAAAAAAAAAAAACCTTGTAATTTCTAGAAGAGTGGCTAGGGGGGTTATTCATTTG  
TATTCAACTAAGGACATATTTACTCATGCTGATGCTCTGTGAGATATTTGAAATTGAACC  
AATGACTACTTAGGATGGGTTGTGGAATAAGTTTTGATGTGGAATTGCACATCTACCTTA  
CAATTACTGACCATCCCCAGTAGACTCCCCAGTCCCATAATTGTGTATCTTCCAGCCAGG  
AATCCTACACGGCCAGCATGTATTTCTACAAATAAAGTTTTCTTTGCATACCAAAAAAAAA  
AAAAAAAAAA

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## FIGURE 286

MKASSLAFSLLSAAFYLLWTPSTGLKTLNLGSCVIATNLQEIRNGFSEIRGSVQAKDGN  
DIRILRRTESLQDTKPANRCCLRHLRLYLDRVFKNYQTPDHYTLRKISSLANSTLIK  
KDLRLSHAHMTCHCGEEAMKKYSQILSHFEKLEPQAAVVKALGELDILLQWMEETE

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**FIGURE 287**

AATGCCCCATGCGCACCCACAGCTCGCGCTCCTGCAAGTGTTCTTTCTGGTGTTCCTCCG  
ATGGCGTCCGGCCTCAGCCCTCTTCCTCCCCATCAGGGGCAGTGCCACGTCCTTTGGAGC  
TGCAGCGAGGGACGGATGGCGGAACCCCTCCAGTCCCCTTCAGAGGCGACTGCAACTCGCC  
CGGCCGTGCCTGGACTCCCTACAGTGGTCCCTACTCTCGTGACTCCCTCGGCCCCCTGGGA  
ATAGGACTGTGGACCTCTTCCCAGTCTTACCGATCTGTGTCTGTGACTTGACTCCTGGAG  
CCTGCGATATAAATTGCTGCTGCGACAGGGACTGCTATCTTCTCCATCCGAGGACAGTTT  
TCTCCTTCTGCCTTCCAGGCAGCGTAAGGTCTTCAAGCTGGGTTTGTGTAGACAACTCTG  
TTATCTTCAGGAGTAATTCCCCGTTTCTTCAAGAGTTTTCATGGATTCTAATGGAATCA  
GGCAGTTTTGTGTCCATGTGAACAACTCAAACCTTAAACTATTTCCAGAAGCTTCAAAAGG  
TCAATGCAACCAACTTCCAGGCCCTGGCTGCAGAGTTTGGAGGCGAATCATTCACTTCAA  
CATTCCAACTCAATCACCACCATCTTTTTACAGGGCTGGGGACCCCATTTCTACTTACT  
TCCCCAAGTGGTCTGTAATAAGCTTGCTGAGACAACCTGCAGGAGTTGGAGCTGGGGGAC  
TCTGTGCTGAAAGCAATCCTGCAGGTTTCTTAGAGAGTAAAAGTACAACTTGCACTCGTT  
TTTTCAAGAACCTGGCTAGTAGCTGTACCTTGGATTGAGCCCTCAATGCTGCCTCTTACT  
ATAACTTTCAGTCTTAAAGGTTCCAAGAAGCATGACTGATCCACAGAATATGGAGTTCC  
AGGTTCTGTAAATACTTACCTCACAGGCTAATGCTCCTCTGTTGGCTGGAAACACTTGT  
AGAATGTAGTTTCTCAGGTCACCTATGAGATAGAGACCAATGGGACTTTTGGAAATCCAGA  
AAGTTTCTGTGAGTTTGGGACAAACCAACCTGACTGTTGAGCCAGGCGCTTCTTACAGC  
AACACTTCATCCTTCGCTTCAGGGCTTTTCAACAGAGCACAGCTGCTTCTCTCACCAGTC  
CTAGAAGTGGGAATCCTGGCTATATAGTTGGGAAGCCACTCTTGGCTCTGACTGATGATA  
TAAGTTACTCAATGACCCTCTTACAGAGCCAGGGTAATGGAAGTTGCTCTGTTAAAAGAC  
ATGAAGTGCAGTTTGGAGTGAATGCAATATCTGGATGCAAGCTCAGGTTGAAGAAGGCAG  
ACTGCAGCCACTTGCAGCAGGAGATTTATCAGACTCTTCATGGAAGGCCAGACCAGAGT  
ATGTTGCCATCTTTGGTAATGCTGACCCAGCCAGAAAGGAGGGTGGACCAGGATCCTCA  
ACAGGCACTGCAGCATTTACAGCTATAAACTGTACTTCTGCTGTCTCATACCAGTTTCCC  
TGGAGATCCAGGTATTGTGGGCATATGTAGGTCTCCTGTCCAACCCGCAAGCTCATGTAT  
CAGGAGTTGATTCCTATACAGTGCAGTCTATACAGGATTCTCAGCAAGTTACAGAAG  
TATCTTTGACAACCTCTGTGAACTTTGTGGACATTACCCAGAAGCCACAGCTCCAAGGG  
GCCAACCCAAAATGGACTGGAAATGGCCATTGACTTCTTCCCTTCAAAGTGGCATTCA  
GCAGAGGAGTATCTCTCAAAAATGCTCAGTCTCTCCCATCCTTATCCTGTGCCTCTTAC  
TACTTGGAGTTCTCAACCTAGAGACTATGTGAAGAAAAGAAAATAATCAGATTTAGTTT  
TCCCTATGAGAACTCTGAGGCAGCCACTTATCTTGGCTAAATAGAACCTCACCTGCTCA  
TGACCAGAGAGCATTTAGGATAATAGATGACCTAACTGAAGGAATCCTTGTATATGAAAG  
GAGTTATTTTAGAAAAGCAATAAAAATATTTTATTTCATCNTAAAAA

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**FIGURE 288**

M RTPQLALLQVFFLVFPDGV RPQPSSSPSGAVPTSLELQRGTDGGTLQSPSEATATRPV  
PGLPTVVPTLVTPSAPGNRTVDLFPVLPIVCDLTPGACDINCCCDRDCYLLHPRTVFSF  
CLPGSVRSSSWVCVDNSVIFRSNSPFP SRVFMDSNGIRQFCVHVNNSNLNYFQKLQKVNA  
TNFQALAAEFGGESFTSTFQTQSPPSFYRAGDPILTYFPKWSVISLLRQPAGVGAGGLCA  
ESNPAGFLESKSTTCTRFFKNLASSCTLDSALNAASYNFTVLKVPRSMTDPQNMEFQVP  
VILTSQANAPLLAGNTCQNVVSQVTYEIETNGTFGIQKVSVSLGQTNLTVEPGASLQQHF  
ILRFRAFQQSTAASLTSPRSGNPGYIVGKPLLALTDDISYSMTLLQSQNGSCSVKRHEV  
QFGVNAISGCKLRLKKADCSHLQQEIIYQTLHGRPRPEYVAIFGNADPAQKGGWTRILNRH  
CSISAINCTSCCLIPVSLEIQVLWAYVGLLSNPQAHVSGVRFLYQCQSIQDSQQVTEVSL  
TTLVNFVDITQKPQPPRGQPKMDWKWPFDFPFKVAFSRGVFSQKCSVSPILILCLLLLG  
VLNLETM

**Important features of the protein:****Signal peptide:**

amino acids 1-22

**Transmembrane domains:**

amino acids 484-505, 581-600

**N-glycosylation sites:**amino acids 78-82, 165-169, 179-185, 279-285, 331-337,  
347-351, 410-414, 487-491**N-myristoylation sites:**

amino acids 30-36, 41-47, 124-130, 232-238, 236-242, 409-415

**Prokaryotic membrane lipoprotein lipid attachment site:**

amino acids 420-431



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**FIGURE 289**

CGCGGAGCCCTGCGCTGGGAGGTGCACGGTGTGCACGCTGGACTGGACCCCCATGCAACC  
CCGCGCCCTGCGCCTTAACCAGGACTGCTCCGCGCGCCCTGAGCCTCGGGCTCCGGCCC  
GGACCTGCAGCCTCCAGGTGGCTGGGAAGAACTCTCCAACAATAAATACATTTGATAAG  
AAAGATGGCTTTAAAAGTGCTACTAGAACAAGAGAAAACGTTTTTCACTCTTTTAGTATT  
ACTAGGCTATTTGT CATGTAAAGTGACTTGTGAATCAGGAGACTGTAGACAGCAAGAATT  
CAGGGATCGGTCTGGAACTGTGTTCCCTGCAACCAGTGTGGGCCAGGCATGGAGTTGTC  
TAAGGAATGTGGCTTCGGCTATGGGGAGGATGCACAGTGTGTGACGTGCCGGCTGCACAG  
GTTCAAGGAGGACTGGGGCTTCAGAAATGCAAGCCCTGTCTGGACTGCGCAGTGGTGAA  
CCGCTTTTCAGAAGGCAAATTGTT CAGCCACCAGTGATGCCATCTGCGGGGACTGCTTGCC  
AGGATTTTATAGGAAGACGAACTTGT CGGCTTTCAAGACATGGAGTGTGTGCCTTGTGG  
AGACCCTCCTCCTCCTTACGAACCGCACTGTGCCAGCAAGGTCAACCTCGTGAAGATCGC  
GTCCACGGCCTCCAGCCCACGGGACACGGCGCTGGCTGCCGTTATCTGCAGCGCTCTGGC  
CACCGTCTCTGGCCCTGCTCATCCTCTGTGT CATCTATTGTAAGAGACAGTTTATGGA  
GAAGAAACCCAGCTGGTCTCTGCGGTGCGAGGACATT CAGTACAACGGCTCTGAGCTGTC  
GTGTTTTGACAGACCTCAGCTCCACGAATATGCCACAGAGCCTGCTGCCAGTGCCGCCG  
TGACTCAGTGCAGACCTGCGGGCCGGTGCGCTTGCTCCCATCCATGTGCTGTGAGGAGGC  
CTGCAGCCCCAACCCGGCGACTCTTGTTGTGGGGTGCACTTCTGCAGCCAGTCTTCAGGC  
AAGAAACGCAAGGCCAGCCGGGGAGATGGTGCCGACTTCTTTCGGATCCCTCACGCAGTC  
CATCTGTGGCGAGTTTTTCAGATGCCTGGCCTCTGATGCAGAATCCCATGGGTGGTGACAA  
CATCTCTTTTTGTGACTCTTATCCTGAACTCACTGGAGAAGACATT CATTCTCTCAATCC  
AGAACTTGAAAGCTCAACGTCTTTGGATTCAAATAGCAGTCAAGATTTGGTTGGTGGGGC  
TGTTCCAGTCCAGTCTCATTCTGAAAACTTTACAGCAGCTACTGATTTATCTAGATATAA  
CAACACACTGGTAGAATCAGCATCAACTCAGGATGCACTAACTATGAGAAGCCAGCTAGA  
TCAGGAGAGTGGCGCTGTCATCCACCCAGCCACTCAGACGTCCCTCCAGGAAGCTTAAAG  
AACCTGCTTCTTTCTGCAGTAGAAGCGTGTGCTGGAACCCAAAGAGTACTCCTTTGTTAG  
GCTTATGGACTGAGCAGTCTGGACCTTG CATGGCTTCTGGGGCAAAAATAAATCTGAACC  
AAACTGACGGCATTGTAAGCCTTTCAGCCAGTTGCTTCTGAGCCAGACCAGCTGTAAGCT  
GAAACCTCAATGAATAACAAGAAAAGACTCCAGGCCGACTCATGATACTCTGCATCTTTC  
CTACATGAGAAGCTTCTCTGCCACAAAAGTGACTTCAAAGACTGATGGGTTGAGCTGGCA  
GCCTATGAGATTGTGGACATATAACAAGAAACAGAAATGCCCTCATGCTTATTTTCATGG  
TGATTGTGGTTTTACAAGACTGAAGACCCAGAGTATACTTTTTCTTTCAGAAATAATTT  
CATAACCGCCTATGAAATATCAGATAAATTACCTTAGCTTTTATGTAGAAATGGGTTCAAAA  
GTGAGTGTCTTATTTGAGAAGGACACTTTTTTCATCATCTAACTGATTTCGCATAGGTGG  
TTAGAATGGCCCTCATATTGCCTGCCTAAATCTTGGGTTTATTAGATGAAGTTTACTGAA  
TCAGAGGAATCAGACAGAGGAGGATAGCTCTTTCAGAAATCCACACTTCTGACCTCAGCC  
TCGGTCTCATGAACACCCGCTGATCTCAGGAGAACACCTGGGCTAGGGAATGTGGTCCGAG  
AAAGGGCAGCCCATTGCCCAGAATTAACACATATTGTAGAGACTTGTATGCAAAGGTTGG  
CATATTTATATGAAAATTAGTTGCTATAGAAACATTTGTTGCATCTGTCCCTCTGCCTGA  
GCTTAGAAGGTTATAGAAAAGGGTATTTATAAACATAAATGACCTTTTACTTGCAATTGT  
ATCTTATACTAAAGGCTTTAGAAATTACAACATATCAGGTTCCCTACTACTGAAGTAGC  
CTTCCGTGAGAACACACCACATGTTAGGACTAGAAGAAAATGCACAAATTTGTAGGGGTTT  
GGATGAAGCAGCTGTAACCTAGTGTAGTTTGACCAGGACATTGTGCTGCTCCTTCC  
AATTGTGTAAGATTAGTTAGCATCATCTCCTACTTTAGCCATCCGGTGTGGATTAA  
GAGGACGGTGCTTCTTTCTATTAAAGTGCTCCATCCCTACCATCTACACATTAGCATTG  
TCTCTAGAGCTAAGACAGAAATTAACCCCGTT CAGTCACAAAGCAGGGAATGGTTTCATTT  
ACTCTTAATCTTTATGCCCTGGAGAAGACCTACTTGAACAGGGCATATTTTTTTAGACTTC  
TGAACATCAGTATGTTTCGAGGGTACTATGATATTTTGGTTTGGAATTGCCCTGCCCAAGT  
CACTGTCTTTTAACTTTTAACTGAATATTAAATGTATCTGTCTTTCCT

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**FIGURE 290**

MALKVLLLEQEKTFFTLLVLLGYLSCKVTCESGDCRQQEFRDRSGNCVPCNQCGPGMELSK  
ECGFGYGEDAQCVTCLHRFKEDWGFQKCKPCLDCAVVNRFQKANCSATSDAICGDCLPG  
FYRKTKLVGFQDMECVPCGDPPPPYEPHCASKVNLVKIASTASSPRDTALAAVIC SALAT  
VLLALLILCVIYCKRQFMKKPSWSLRSQDIQYNGSELSCFDRPQLHEYAHRACCQCRRD  
SVQTCGPVRLLP SMCCEEACSPNPATLGCGVHSAASLQARNAGPAGEMVPTFFGSLTQSI  
CGEFSDAWPLMQNPMGGDNISFCDSYPELTGEDIHSLNPELESSTSLDSNSSQDLVGGAV  
PVQSHSENF TAATDLSRYNNTLVESASTQDALTMRSQLDQESGAVIHPATQTSLQEA

**Important features of the protein:**

**Signal peptide:**

Amino acids 1-25

**Transmembrane domain:**

Amino acids 169-192

**N-glycosylation sites:**

Amino acids 105-109; 214-218; 319-323; 350-354; 368-372; 379-383

**cAMP- and cGMP-dependent protein kinase phosphorylation sites:**

Amino acids 200-204; 238-242

**Tyrosine kinase phosphorylation site:**

Amino acids 207-214

**N-myristoylation sites:**

Amino acids 55-61; 215-221; 270-276

**Prokaryotic membrane lipoprotein lipid attachment site:**

Amino acids 259-270

**TNFR/NGFR family cysteine-rich region proteins:**

Amino acids 89-96

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**FIGURE 291**

CCTGGAGCCGGAAGCGCGGCTGCAGCAGGGCGAGGCTCCAGGTGGGGTTCGGTTCGCGCATC  
CAGCCTAGCGTGTCCACGATGCGGCTGGGCTCCGGGACTTTTCGCTACCTGTTGCGTAGCG  
ATCGAGGTGCTAGGGATCGCGGTCTTCCTTCGGGGATTCTTCCCGGCTCCCGTTCGTTCC  
TCTGCCAGAGCGGAACACGGAGCGGAGCCCCAGCGCCCGAACCCTCGGCTGGAGCCAGT  
TCTAACTGGACCACGCTGCCACCACCTCTCTTCAGTAAAGTTGTTATTGTTCTGATAGAT  
GCCTTGAGAGATGATTTTGTGTTTGGGTCAAAGGGTGTGAAATTTATGCCCTACACAAC  
TACCTTGTGGAAAAGGAGCATCTCACAGTTTGTGGCTGAAGCAAAGCCACCTACAGTT  
ACTATGCCTCGAATCAAGGCATTGATGACGGGAGCCTTCCTGGCTTTGTGACGTCATC  
AGGAACCTCAATTCTCCTGCACTGCTGGAAGACAGTGTGATAAGACAAGCAAAGCAGCT  
GGAAAAGAATAGTCTTTTATGGAGATGAAACCTGGGTAAATTTATCCCAAAGCATT  
GTGGAATATGATGGAACAACCTCATTTTTTCGTGTGATGATTACACAGAGGTGGATAATAAT  
GTCACGAGGCATTTGGATAAAGTATTAAAAAGAGGAGATTGGGACATATTAATCCTCCAC  
TACCTGGGGCTGGACCACATTGGCCACATTTAGGGCCCAACAGCCCCCTGATTGGGCAG  
AAGCTGAGCGAGATGGACAGCGTGCTGATGAAGATCCACACCTCACTGCAGTCGAAGGAG  
AGAGAGACGCCTTTACCCAATTTGCTGGTTCTTTGTGGTGACCATGGCATGTCTGAAACA  
GGAAGTCACGGGGCCTCCTCCACCGAGGAGGTGAATACACCTCTGATTTTAATCAGTTCT  
GCGTTTGAAAGGAAACCCGGTGATATCCGACATCCAAAGCACGTCCAATAGACGGATGTG  
GCTGCGACACTGGCGATAGCACTTGGCTTACCGATTCCAAAAGACAGTGTAGGGAGCCTC  
CTATTCCCAGTTGTGGAAGGAAGACCAATGAGAGAGCAGTTGAGATTTTACATTTGAAT  
ACAGTGCAGCTTAGTAACTGTTGCAAGAGAATGTGCCGTCATATGAAAAGATCCTGGG  
TTTGAGCAGTTTAAAATGTCAGAAAGATTGCATGGGAACTGGATCAGACTGTACTTGGAG  
GAAAAGCATTGAGAAGTCTATTCAACCTGGGCTCCAAGGTTCTCAGGCAGTACCTGGAT  
GCTCTGAAGACGCTGAGCTTGTCCCTGAGTGCACAAGTGGCCCAGTTCTCACCCTGCTCC  
TGCTCAGCGTCCCACAGGCACTGCACAGAAAGGCTGAGCTGGAAGTCCCACTGTCTCTC  
CTGGGTTTTCTGCTCTTTTATTTGGTGATCCTGGTTCTTTCCGGCCGTTACGTCATTG  
TGTGCACCTCAGCTGAAAGTTTCGTGCTACTTCTGTGGCCTCTCGTGGCTGGCGGCAGGCT  
GCCTTTCGTTTACCAGACTCTGGTTGAACACCTGGTGTGTGCCAAGTGTGTCAGTGCCC  
TGGACAGGGGGCCTCAGGGAAGGACGTGGAGCAGCCTTATCCCAGGCCTCTGGGTGTCCC  
GACACAGGTGTTACATCTGTGCTGTGAGGTGAGTGCCTCAGTTCTTGGAAAGCTAGGT  
TCCTGCGACTGTTACCAAGGTGATTGTAAGAGCTGGCGGTCACAGAGGAACAAGCCCCC  
CAGCTGAGGGGGTGTGTGAATCGGACAGCCTCCAGCAGAGGTGTGGGAGCTGCAGCTGA  
GGGAAGAAGAGACAATCGGCCTGGACACTCAGGAGGGTCAAAGGAGACTTGGTTCGCACC  
ACTCATCCTGCCACCCCCAGAATGCATCCTGCCTCATCAGGTCCAGATTTCTTTCCAAGG  
CGGACGTTTTCTGTTGGAATTCTTAGTCCTTGGCCTCGGACACCTTCATTTCGTTAGCTGG  
GGAGTGGTGGTGAGGCAGTGAAGAAGAGGCGGATGGTCACTCAGATCCACAGAGCCCA  
GGATCAAGGGACCCACTGCAGTGGCAGCAGGACTGTTGGGCCCCCACCCTGCAC  
AGCCCTCATCCCCCTCTTGGCTTGAGCCGTGAGAGGCCCTGTGCTGAGTGTCTGACCGAGA  
CACTCACAGCTTTGTGATCAGGGCACAGGCTTCCTCGGAGCCAGGATGATCTGTGCCACG  
CTTGACCTCGGGCCCATCTGGGCTCATGCTCTCTCTCCTGCTATTGAATTAGTACCTAG  
CTGCACACAGTATGTAGTTACCAAAGAATAAACGGCAATAATTGAGAAAAAAA

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**FIGURE 292**

MRLGSGTFATCCVAIEVLGIAVFLRGFFPAPVRSSARAEGHGAEPPEPSAGASSNWTTL  
PPPLFSKVVIVLIDALRDDFVFGSKGVKFMPYTTYLVEKGASHSFVAEAKPPTVTMPRIK  
ALMTGSLPGFVDVIRNLNSPALLEDVIRQAKAAGKRIVFYGDETWVKLFPKHFVEYDGT  
TSFFVSDYTEVDNNVTRHLDKVLKRGDWDILILHYLGLDGHIGHISGPN SPLIGQKLSEMD  
SVLMKIHTSLQSKERETPLPNLLVLCGDHGMSETGSHGASSTEEVNTPLILISSAFERKP  
GDIRHPKHVQ

**Important features of the protein:**

**Signal peptide:**

amino acids 1-34

**Transmembrane domain:**

amino acids 58-76

**N-glycosylation sites:**

amino acids 56-60, 194-198

**N-myristoylation sites:**

amino acids 6-12, 52-58, 100-106, 125-131, 233-239, 270-276,  
275-281, 278-284

**Amidation site:**

amino acids 154-158

**Cell attachment sequence:**

amino acids 205-208

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**FIGURE 293**

AGCCAGGCAGCACATCACAGCGGGAGGAGCTGTCCCAGGTGGCCCAGCTCAGCAATGGCA  
ATGGGGGTCCCCAGAGTCATTCTGCTCTGCCTCTTTGGGGCTGCGCTCTGCCTGACAGGG  
TCCCAAGCCCTGCAGTGCTACAGCTTTGAGCACACCTACTTTGGCCCCCTTGACCTCAGG  
GCCATGAAGCTGCCCAGCATCTCCTGTCTCATGAGTGCTTTGAGGCTATCCTGTCTCTG  
GACACCGGGTATCGCGCGCCGGTGACCTGGTGCGGAAGGGCTGCTGGACCGGGCCTCCT  
GCGGGCCAGACGCAATCGAACCCGGACGCGCTGCCGCCAGACTACTCGGTGGTGCGCGGC  
TGCACAACTGACAAATGCAACGCCACCTCATGACTCATGACGCCCTCCCCAACCTGAGC  
CAAGCACCCGACCCGCGGACGCTCAGCGGCGCCGAGTGCTACGCCTGTATCGGGGTCCAC  
CAGGATGACTGCGCTATCGGCAGGTCCCGACGAGTCCAGTGTCACCAGGACCAGACCGCC  
TGCTTCCAGGGCAGTGGCAGAATGACAGTTGGCAATTTCTCAGTCCCTGTGTACATCAGA  
ACCTGCCACCGGCCCTCCTGCACCACCGAGGGCACCACCAGCCCCCTGGACAGCCATCGAC  
CTCCAGGGCTCCTGCTGTGAGGGGTACCTCTGCAACAGGAAATCCATGACCCAGCCCTTC  
ACCACTGCTTCAGCCACCACCCCTCCCCGAGCACTACAGGTCTTGGCCCTGCTCCTCCCA  
GTCCTCCTGCTGGTGGGGCTCTCAGCATAGACCGCCCCTCCAGGATGCTGGGGACAGGGC  
TCACACACCTCATTCTTGCTGCTTCAGCCCCTATCACATAGCTCACTGGAAAATGATGTT  
AAAGTAAGAATTGCAAAA

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**FIGURE 294**

MAMGVPRVILLCLFGAALCLTGSQALQCYSFEHTYFGPFDLRAMKLPSISCPHECFEAIL  
SLDTGYRAPVTLVRKGCWTGPPAGQTQSNPDALPPDYSVVRGCTTDKCNAHLMTHDALPN  
LSQAPDPPTLSGAECYACIGVHQDDCAIGRSRRVQCHQDQTACFQSGRMTVGNFSPVY  
IRTCHRPSCCTTEGTTSPWTAIDLQSCCEGYLCNRKSMTQPFTSASATTPPRALQVLALL  
LPVLLLVLGLSA

**Important features of the protein:**

**Signal peptide:**

amino acids 1-19

**Transmembrane domain:**

amino acids 233-251

**N-glycosylation sites:**

amino acids 120-124, 174-178

**N-myristoylation sites:**

amino acids 15-21, 84-90

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**FIGURE 295**

AATCGGCTGATTCTGCATCTGGAACTGCCTTCATCTTGAAAGAAAAGCTCCAGGTCCCT  
TCTCCAGCCACCCAGCCCCAAGATGGTGATGCTGCTGCTGCTGCTTTCCGCACTGGCTGG  
CCTCTTCGGTGCGGCAGAGGGACAAGCATTTCATCTTGGGAAGTGCCCCAATCCTCCGGT  
GCAGGAGAATTTTGACGTGAATAAGTATCTCGGAAGATGGTACGAAATTGAGAAGATCCC  
AACCAACCTTTGAGAATGGACGCTGCATCCAGGCCAACTACTCACTAATGGAAAACGGAAA  
GATCAAAGTGTTAAACCAGGAGTTGAGAGCTGATGGAAGTGTGAATCAAATCGAAGGTGA  
AGCCACCCCAGTTAACCTCACAGAGCCTGCCAAGCTGGAAGTTAAGTTTTCTGGTTTTAT  
GCCATCGGCACCGTACTGGATCCTGGCCACCGACTATGAGAACTATGCCCTCGTGTATTC  
CTGTACCTGCATCATCCAACTTTTTCACGTGGATTTTGCTTGGATCTTGGCAAGAAACCC  
TAATCTCCCTCCAGAAACAGTGGACTCTCTAAAAAATATCCTGACTTCTAATAACATTGA  
TGTCAAGAAAATGACGGTCACAGACCAGGTGAACTGCCCCAAGCTCTCGTAAACCAGGTTT  
TACAGGGAGGCTGCACCCACTCCATGTTACTTCTGCTTCGCTTTCCCCTACCCCACCCCC  
CCCCATAAAGACAAACCAATCAACCACGACAAAGGAAGTTGACCTGAACATGTAACCAT  
GCCCTACCCTGTTACCTTGCTAGCTGCAAAATAAACTTGTTGCTGACCTGCTGTGCTCGC  
AAAAAA

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**FIGURE 296**

MVMLLLLLSALAGLFGAAEGQAFHLGKCPNPPVQENFDVNKYLGRWYEIEKIPTTFENG  
RCIQANYSLMENGKIKVLNQELRADGTVNQIEGEATPVNLTEPAKLEVKFSWFMPSPY  
WILATDYENYALVYSCTCIIQLFHVDFAWILARNPNLPPETVDSLKNILTSNNIDVKKM  
TVTDQVNCPKLS

**Signal sequence:**

1-16

**N-glycosylation site:**

65-68

98-101

**cAMP- and cGMP-dependent protein kinase phosphorylation site:**

175-178

**N-myristoylation site:**

13-18

16-21

**Lipocalin proteins:**

36-47

120-130

**Lipocalin / cytosolic fatty-acid binding proteins:**

41-185



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**FIGURE 297**

GGGTGATTGAACTAAACCTTCGCCGCACCGAGTTTGCAGTACGGCCGTCACCCGCACCGC  
TGCCTGCTTGCGGTTGGAGAAATCAAGGCCCTACCGGGCCTCCGTAGTCACCTCTCTATA  
GTGGGCGTGGCCGAGGCCGGGGTGACCCTGCCGGAGCCTCCGCTGCCAGCGACATGTTCA  
AGGTAATTCAGAGGTCCGTGGGGCCAGCCAGCCTGAGCTTGCTCACCTTCAAAGTCTATG  
CAGCACCAAAAAAGGACTCACCTCCAAAAATTCCGTGAAGGTTGATGAGCTTCACTCT  
ACTCAGTTCCTGAGGGTCAATCGAAGTATGTGGAGGAGGCAAGGAGCCAGCTTGAAGAAA  
GCATCTCACAGCTCCGACACTATTGCGAGCCATACACAACCTGGTGTGAGGAAACGTACT  
CCCAAACCTAAGCCCAAGATGCAAAGTTTGGTTCAATGGGGGTTAGACAGCTATGACTATC  
TCCAAAATGCACCTCCTGGATTTTTTCCGAGACTTGGTGTATTGGTTTTGCTGGCCTTA  
TTGGACTCCTTTTGGCTAGAGGTTCAAAAATAAAGAAGCTAGTGTATCCGCCTGGTTTCA  
TGGGATTAGCTGCCTCCCTCTATTATCCACAACAAGCCATCGTGTTTGCCAGGTCAGTG  
GGGAGAGATTATATGACTGGGGTTTACGAGGATATATAGTCATAGAAGATTTGTGGAAGG  
AGAACTTTCAAAGCCAGGAAATGTGAAGAATTCACCTGGAACCTAAGTAGAAAACTCCAT  
GCTCTGCCATCTTAATCAGTTATAGGTAAACATTGGAACTCCATAGAATAAATCAGTAT  
TTCTACAGAAAAATGGCATAGAAGTCAGTATTGAATGTATTAAATTGGCTTTCTTCTTCA  
GGAAAACTAGACCAGACCTCTGTTATCTTCTGTGAAATCATCCTACAAGCAAACCTAACC  
TGGAATCCCTTCACCTAGAGATAATGTACAAGCCTTAGAACTCCTCATTTCTCATGTTGCT  
ATTTATGTACCTAATTAAAACCCAAGTTTAAAAAAAAAAAAAAAAAAAAAAAAAAAAA  
AAAAAAA

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**FIGURE 298**

MFKVIQRSVGPASLSLLTFKVYAAPKKDSPPKNSVKVDELSLYSVPEGQSKYVEEARSQ  
EESISQLRHYCEPYTTWCQETYSQTKPKMQSLVQWGLDSYDYLQNAAPPGFFPRLGVIGFA  
GLIGLLLARGSKIKKLVYPPGFMGLAASLYYPQQAIVFAQVSGERLYDWGLRGYIVIEDL  
WKENFQKPGNVKNSPGTK

**Important features:****Signal peptide:**

Amino acids 1-23

**Transmembrane domain:**

Amino acids 111-130

**cAMP- and cGMP-dependent protein kinase phosphorylation site:**

Amino acids 26-30

**Tyrosine kinase phosphorylation site:**

Amino acids 36-44

**N-myristoylation sites:**

Amino acids 124-130;144-150;189-195

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**FIGURE 299**

CCGCTGAGATGTACGAACTTCCGGTTCTCCGGGCAGCTGCCACTGCTGTAGCTTCTGCCA  
CCTGCCACGACCGGGCCTCTCCCTGGCGTTTGGTCACCTCTGCTTCATTCTCCACCGCGC  
CTATGGTCCCTCTTGGAGCCAGCGTGGCGGGCCTGGCGGCTCCCGGGTGGTGAGAGAGCG  
GTCCGGGAACGATGAAGGCCTCGCAGTGCTGCTGCTGTCTCAGCCACCTCTTGGCTTCCG  
TCCTCCTCCTGCTGTTGCTGCCTGAACCTAAGCGGGCCCCCTGGCAGTCCTGCTGCAGGCAG  
CCGAGGCCCGCGCCAGGTCTTGGGCCTCCTGACCCTAGACCACGGACATTACCGCCGCTGC  
CACCGGGCCCTACCCCTGCCCAGCAGCCGGGCGGTGGTCTGGCTGAAGCTGCGGGGCGCG  
GGGGCTCCGAGGGAGGCAATGGCAGCAACCCTGTGGCCGGGCTTGAGACGGACGATCACG  
GAGGGAAGGCCGGGGAAGGCTCGGTGGGTGGCGGCCCTTGCTGTGAGCCCCAACCTGGCG  
ACAAGCCCATGACCCAGCGGGCCCTGACCGTGTGATGGTGGTGAGCGGCGCGGTGCTGG  
TGTACTTCGTGGTCAGGACGGTCAGGATGAGAAGAAGAAACCGAAAGACTAGGAGATATG  
GAGTTTGGACACTAACATAGAAAATATGGAATTGACACCTTTAGAACAGGATGATGAGG  
ATGATGACAACACGTTGTTTGATGCCAATCATCCTCGAAGATAAGAATGTGCCTTTTGAT  
GAAAGAACTTTATCTTTCTACAATGAAGAGTGAATTTCTATGTTTAAGGAATAAGAAGC  
CACTATATCAATGTTGGGGGGGTATTTAAGTTACATATATTTTAACAACCTTTAATTTGC  
TGTTGCAATAAATACCGTATCCTTTTATTATATCTTTATATGTATAGAAGTACTCTATTA  
ATGGGCTCAGAGATGTTGGGGATAAAGTATACTGTAATAATTTATCTGTTTGAAAATTAC  
TATAAAACGGTGTTTTCTGGTCGGTTTTTGTTCCTGCTTACCATATGATTGTAAATTGT  
TTTATGTATTAATCAGTTAATGCTAATTATTTTGCTGATGTCATATGTTAAAGAGCTAT  
AAATTCCAACAACCAACTGGTGTGTAATAAATAATTTAAATTTTCTTTACTGAAAGGTAT  
TTCCCATTTTTGTGGGGAAAAGAAGCCAAATTTATTACTTTGTGTTGGGGTTTTTAAAT  
ATTAAGAAATGTCTAAGTTATTGTTTGCAAAACAATAAATATGATTTTAAATTCTCTTAA  
AAAAAAA

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**FIGURE 300**

MKASQCCCLSHLLASVLLLLLLPELSGPLAVLLQAAEAAPGLGPPDPRPRTLPPPLPPGP  
TPAQQPGRGLAEAAGPRGSEGGNGSNPVAGLETDDHGGKAGEGSVGGGLAVSPNPGDKPM  
TQRALTVLMVVS GAVLVYFVVRTVRMRRRNKTRRYGVLD TN IENMELTPLEQDDEDDDN  
TLFDANHPRR

**Signal peptide:**  
amino acids 1-28

**Transmembrane domain:**  
amino acids 124-140

**N-glycosylation site:**  
amino acids 83-87

**N-myristoylation sites:**  
amino acids 69-75, 78-84, 81-87, 97-103, 103-109, 106-112;  
157-160

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**FIGURE 301**

CTCGGCTGGATTTAAGGTTGCCGCTAGCCGCTGGGAATTTAAGGGACCCACACTACCTT  
CCCGAAGTTGAAGGCAAGCGGTGATTGTTTGTAGACGGCGCTTTGTCATGGGACCTGTGC  
GGTTGGGAATATTGCTTTTTCCTTTTGGCCGTGCACGAGGCTTGGGCTGGGATGTTGA  
AGGAGGAGGACGATGACACAGAACGCTTGCCAGCAAATGCGAAGTGTGTAAGCTGCTGA  
GCACAGAGCTACAGGCGGAAGTGAAGTGCACCGGTGATCTCGAGAGGTGCTGGAGCTGG  
GGCAGGTGCTGGATACAGGCAAGAGGAAGAGACACGTGCCTTACAGCGTTTCAGAGACAA  
GGCTGGAAGAGGCCCTTAGAGAATTTATGTGAGCGGATCCTGGACTATAGTGTTACGCTG  
AGCGCAAGGGCTCACTGAGATATGCCAAGGGTCAGAGTCAGACCATGGCAACACTGAAAG  
GCCTAGTGCAGAAGGGGGTGAAGGTGGATCTGGGGATCCCTCTGGAGCTTTGGGATGAGC  
CCAGCGTGGAGGTACATACCTCAAGAAGCAGTGTGAGACCATGTTGGAGGAGTTTGAAG  
ACATTGTGGGAGACTGGTACTTCCACCATCAGGAGCAGCCCCTACAAAATTTCTCTGTG  
AAGGTCATGTGCTCCCAGCTGCTGAAACTGCATGTCTACAGGAACTTGGACTGGAAAGG  
AGATCACAGATGGGGAAGAGAAAAACAGAAGGGGAGGAAGAGCAGGAGGAGGAGGAGGAAG  
AGGAGGAAGAGGAAGGGGGAGACAAGATGACCAAGACAGGAAGCCACCCCAAACCTTGACC  
GAGAAGATCTTTGACCCTTGCCCTTGAGCCCCCAGGAGGGGAAGGGATCATGGAGAGCCC  
TCTAAAGCCTGCACTCTCCCTGCTCCACAGCTTTCAGGGTGTGTTTATGAGTGACTCCAC  
CCAAGCTTGTAGCTGTTCTCTCCCATCTAACCTCAGGCAAGATCCTGGTGAAACAGCATG  
ACATGGCTTCTGGGGTGGAGGGTGGGGGTGGAGGTCCTGCTCCTAGAGATGAACTCTATC  
CAGCCCCTTAATTGGCAGGTGTATGTGCTGACAGTACTGAAAGCTTTCCTCTTTAACTGA  
TCCCACCCCAACCCAAAAGTCAGCAGTGGCACTGGAGCTGTGGGCTTTGGGGAAGTCACT  
TAGCTCCTTAAGGTCTGTTTTTAGACCCTTCCAAGGAAGAGGCCAGAACGGACATTCTCT  
GCGATCTATATACATTGCCTGTATCCAGGAGGCTACACACCAGCAAACCGTGAAGGAGAA  
TGGGACACTGGGTGATGGCCTGGAGTTGCTGATAATTTAGGTGGGATAGATACTTGGTCT  
ACTTAAGCTCAATGTAACCCAGAGCCCACCATATAGTTTTATAGGTGCTCAACTTTCTAT  
ATCGCTATTAAACTTTTTTCTTTTTTTCTA

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**FIGURE 302**

MGPVRLGILLFLFLAVHEAWAGMLKEEDDDTERLPSKCEVCKLLSTELQAELSR TGRSRE  
VLELGQVLDTGKRKRHVPYSVSETRLEEALENLCERILDYSVHAERKGSRLRYAKGQSQTM  
ATLKGLVQKGVKVDLGIPLELWDEPSVEV TYLKKQCETMLEEFEDIVGDWYFHHQEQLQ  
NFLCEGHVLPAAETACLQETWTGKEITDGEEKTEGEEEQEEEEEEEEEEEEGGDKMTKTGSH  
PKLDREDL

**Important features of the protein:**

**Signal peptide:**

amino acids 1-21

**cAMP- and cGMP-dependent protein kinase phosphorylation site:**

amino acids 106-110

**N-myristoylation site:**

amino acids 115-121

**Amidation site:**

amino acids 70-74

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**FIGURE 303**

CTCCTGCACTAGGCTCTCAGCCAGGGATGATGCGCTGCTGCCGCCGCCGCTGCTGCTGCC  
GGCAACCACCCCATGCCCTGAGGCCGTTGCTGTTGCTGCCCCCTCGTCCTTTTACCTCCCC  
TGGCAGCAGCTGCAGCGGGCCCAAACCGATGTGACACCATATACCAGGGCTTCGCCGAGT  
GTCTCATCCGCTTGGGGGACAGCATGGGCCCGGAGGCGAGCTGGAGACCATCTGCAGGT  
CTTGGAATGACTTCCATGCCTGTGCCTCTCAGGTCCTGTCAGGCTGTCCGGAGGAGGCAG  
CTGCAGTGTGGGAATCACTACAGCAAGAAGCTCGCCAGGCCCCCCCGTCCGAATAACTTGC  
ACACTCTGTGCGGTGCCCCGGTGCATGTTGCGGAGCGCGGCACAGGCTCCGAAACCAACC  
AGGAGACGCTGCGGGCTACAGCGCCTGCACTCCCCATGGCCCCCTGCGCCCCCACTGCTGG  
CGGCTGCTCTGGCTCTGGCCTACCTCCTGAGGCCTCTGGCCTAGCTTGTGTTGGGTTGGGTA  
GCAGCGCCCGTACCTCCAGCCCTGCTCTGGCGGTGGTTGTCCAGGCTCTGCAGAGCGCAG  
CAGGGCTTTTCATTAAAGGTATTTATATTTGTA

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## FIGURE 304

MMRCCRRRCCCRQPPHALRPLLLLLPLVLLPPLAAAAAGPNRCDTIYQGFAECLIRLGDSM  
GRGGELETICRSWNDFHACASQVLSGCPEEAAAVWESLQQEARQAPRPNNLHTLCGAPVH  
VRERGTGSETNQETLRATAPALPMAPAPPLLAAALALAYLLRPLA

Signal peptide:  
Amino acids 1-35

Transmembrane domain:  
Amino acids 141-157

N-myristoylation site:  
Amino acids 127-133

Prokaryotic membrane lipoprotein lipid attachment site:  
Amino acids 77-88



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**FIGURE 305**

AAGTACTTGTGTCCGGGTGGTGGACTGGATTAGCTGCGGAGCCCTGGAAGCTGCCTGTCC  
TTCTCCCTGTGCTTAACCAGAGGTGCCCATGGGTGGACAATGAGGCTGGTCACAGCAGC  
ACTGTTACTGGGTCTCATGATGGTGGTCACTGGAGACGAGGATGAGAACAGCCCGTGTGC  
CCATGAGGCCCTCTTGGACGAGGACACCCTCTTTTGCCAGGGCCTTGAAGTTTCTACCC  
AGAGTTGGGGAACATTGGCTGCAAGGTTGTTCCCTGATTGTAACAACCTACAGACAGAAGAT  
CACCTCCTGGATGGAGCCGATAGTCAAGTTCCCGGGGGCCGTGGACGGCGCAACCTATAT  
CCTGGTGATGGTGGATCCAGATGCCCCTAGCAGAGCAGAACCAGACAGAGATTCTGGAG  
ACATTGGCTGGTAACAGATATCAAGGGCGCCGACCTGAAGAAAGGGAAGATTCAGGGCCA  
GGAGTTATCAGCCTACCAGGCTCCCTCCCCACCGGCACACAGTGGCTTCCATCGCTACCA  
GTTCTTTGTCTATCTTCAGGAAGGAAAAGTCATCTCTCTCCTTCCCAAGGAAAACAAAAC  
TCGAGGCTCTTGGAATGGACAGATTTCTGAACCGCTTCCACCTGGGCGAACCTGAAGC  
AAGCACCCAGTTCATGACCCAGAACTACCAGGACTCACCAACCCTCCAGGCTCCAGAGG  
AAGGGCCAGCGAGCCCAAGCACAAAACCAGGCAGAGATAGCTGCCTGCTAGATAGCCGGC  
TTTGCCATCCGGGCATGTGGCCACACTGCTCACCACCGACGATGTGGGTATGGAACCCCC  
TCTGGATACAGAACCCCTTCTTTTCCAAATTAAAAAAAAAAATCATCAA

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**FIGURE 306**

MGWTMRLVTAALLLGLMMVVTGDEDENSPCAHEALLDEDTLFCQGLEVFYPELGNIGCKV  
VPDCNNYRQKITSWMEPIVKFPGAVDGATYILVMVDPDAPSRAEPRQRFWRHVLVTDIKG  
ADLKKGKIQGQELSAYQAPSPPAHSGFHRYQFFVYLQEGKVISLLPKENKTRGSWKMDRF  
LNRFFHLGEPEASTQFMTQNYQDSPTLQAPRGRASEPKHKTRQR

**Important features of the protein:**

**Signal peptide:**

amino acids 1-22

**N-glycosylation site:**

amino acids 169-173

**Tyrosine kinase phosphorylation site:**

amino acids 59-68

**N-myristoylation sites:**

amino acids 54-60, 83-89, 130-136

**Phosphatidylethanolamine signature:**

amino acids 113-157

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**FIGURE 307**

AAGGAGCAGCCCGCAAGCACCAAGTGAGAGGCATGAAGTTACAGTGTGTTTCCCTTTGGC  
TCCTGGGTACAATACTGATATTGTGCTCAGTAGACAACCACGGTCTCAGGAGATGTCTGA  
TTTCCACAGACATGCACCATATAGAAGAGAGTTTCCAAGAAATCAAAAGAGCCATCCAAG  
CTAAGGACACCTTCCCAAATGTCACTATCCTGTCCACATTGGAGACTCTGCAGATCATTA  
AGCCCTTAGATGTGTGCTGCGTGACCAAGAACCTCCTGGCGTTCTACGTGGACAGGGTGT  
TCAAGGATCATCAGGAGCCAAACCCCAAAATCTTGAGAAAAATCAGCAGCATTGCCAACT  
CTTTCCTCTACATGCAGAAAACCTCTGCGGCAATGTCAGGAACAGAGGCAGTGTCACTGCA  
GGCAGGAAGCCACCAATGCCACCAGAGTCATCCATGACAACCTATGATCAGCTGGAGGTCC  
ACGCTGCTGCCATTAAATCCCTGGGAGAGCTCGACGTCTTCTAGCCTGGATTAATAAGA  
ATCATGAAGTAATGTTCTCAGCTTGATGACAAGGAACCTGTATAGTGATCCAGGGATGAA  
CACCCCCTGTGCGGTTTACTGTGGGAGACAGCCCACCTTGAAGGGGAAGGAGATGGGGAA  
GGCCCCTTGCAGCTGAAAGTCCCACTGGCTGGCCTCAGGCTGTCTTATTCCGCTTGAAAA  
TAGGCAAAAAGTCTACTGTGGTATTTGTAATAAACTCTATCTGCTGAAAGGGCCTGCAGG  
CCATCCTGGGAGTAAAGGGCTGCCTTCCCATCTAATTTATTGTAAAGTCATATAGTCCAT  
GTCTGTGATGTGAGCCAAGTGATATCCTGTAGTACACATTGTACTGAGTGGTTTTTCTGA  
ATAAATTCATATTTTACCTATGA

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**FIGURE 308**

MKLQCVSLWLLGTILILCSVDNHGLRRCLISTDMHHIEESFQEIKRAIQAKDTFPNVTIL  
STLETLQIIKPLDVCCVTKNLLAFYVDRVFKDHQEPNPKILRKISSIANSFLYMQKTLRQ  
CQEQRQCHCRQEATNATRVIHNDNYDQLEVHAAAIKSLGELDVFLAWINKNHEVMFSA

**Signal sequence:**  
amino acids 1-18

**N-glycosylation sites:**  
amino acids 56-60, 135-139

**cAMP- and cGMP-dependent protein kinase phosphorylation site:**  
amino acids 102-106

**N-myristoylation site:**  
amino acids 24-30

**Actinin-type actin-binding domain signature 1:**  
amino acids 159-169

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**FIGURE 309**

GTGACCCACGCGTCCGAAGCTGCTGGAGCCACGATTTCAGTCCCCTGGACTGTAGATAAA  
GACCCTTTCTTGCCAGGTGCTGAGACAACCACACTATGAGAGGCACCTCCAGGAGACGCTG  
ATGGTGGAGGAAGGGCCGTCTATCAATCAATCACTGTTGCTGTTATCACATGCAAGTATC  
CAGAGGCTCTTGAGCAAGGCAGAGGGGATCCCATTTATTTGGGAATCCAGAATCCAGAAA  
TGTGTTTGTATTGTGAGAAGGTTGGAGAACAGCCACATTGCAGCTAAAAGAGCAGAAGA  
TCATGGATCTGTATGGCCAACCCGAGCCCGTGAAACCTTCCTTTCTACCGTGCCAAGA  
CTGGTAGGACCTCCACCCTTGAGTCTGTGGCCTTCCCGGACTGGTTCATTGCCTCCTCCA  
AGAGAGACCAGCCCATCATTCTGACTTCAGAACTTGGGAAGTCATACAACACTGCCTTTG  
AATTAAATATAAATGACTGAACTCAGCCTAGAGGTGGCAGCTTGGTCTTTGTCTTAAAGT  
TTCTGGTTCCCAATGTGTTTTCGTCTACATTTTCTTAGTGTCATTTTCACGCTGGTGCTG  
AGACAGGAGCAAGGCTGCTGTTATCATCTCATTTTATAATGAAGAAGAAGCAATTACTTC  
ATAGCAACTGAAGAACAGGATGTGGCCTCAGAAGCAGGAGAGCTGGGTGGTATAAGGCTG  
TCCTCTCAAGCTGGTGCTGTGTAGGCCACAAGGCATCTGCATGAGTGACTTTAAGACTCA  
AAGACCAAACACTGAGCTTTCTTCTAGGGGTGGGTATGAAGATGCTTCAGAGCTCATGCG  
CGTTACCCACGATGGCATGACTAGCACAGAGCTGATCTCTGTTTCTGTTTTGCTTTATTC  
CCTCTGGGATGATATCATCCAGTCTTTATATGTTGCCAATATACCTCATTGTGTGTAAT  
AGAACCTTCTTAGCATTAAAGACCTTGTAACAAAAATAATTCTTGGGGTGGGTATGAAGA  
TGCTTCAGAGCTCATGCGCGTTACCCACGATGGCATGACTAGCACAGAGCTGATCTCTGT  
TTCTGTTTTGCTTTATTCCTCTTGGGATGATATCATCCAGTCTTTATATGTTGCCAATA  
TACCTCATTGTGTGTAATAGAACCTTCTTAGCATTAAAGACCTTGTAACAAAAATAATTC  
TTGTGTTAAGTTAAATCATTTTTGTCCTAATTGTAATGTGTAATCTTAAAGTTAAATAAA  
CTTTGTGTATTTATATAATAATAAAGCTAAAACCTGATATAAAATAAAGAAAGAGTAAACTG

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## FIGURE 310

MRGTPGDADGGGRAVYQSITVAVITCKYPEALEQGRGDPIYLGIONPEMCLYCEKVGEQP  
TLQLKEQKIMDLYGQPEPVKPFIFYRAKTGRTSTLESVAFPDWFIASSKRDQPIILTSEL  
GKSYNTAFELNIND

**Signal sequence:**  
amino acids 1-17

**N-myristoylation site:**  
amino acids 10-16

**Cell attachment sequence:**  
amino acids 36-39

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**FIGURE 311**

GCGAGGCTGCACCAGCGCCTGGCACCATGAGGACGCCTGGGCCTCTGCCCCGTGCTGCTGC  
TGCTCCTGGCGGGAGCCCCGCGCGCGGCCCACTCCCCGACCTGCTACTCCCGCATGC  
GGGCCCTGAGCCAGGAGATCACCCGCGACTTCAACCTCCTGCAGGTCTCGGAGCCCTCGG  
AGCCATGTGTGAGATACCTGCCCAGGCTGTACCTGGACATAACAATTACTGTGTGCTGG  
ACAAGCTGCGGGACTTTGTGGCCTCGCCCCGTGTTGGAAAGTGGCCCAGGTAGATTCCCT  
TGAAGGACAAAGCACGGAAGCTGTACACCATCATGAACTCGTTCTGCAGGAGAGATTGG  
TATTCCTGTTGGATGACTGCAATGCCTTGGAATACCCAATCCCAGTGACTACGGTCCTGC  
CAGATCGTCAGCGCTTAAGGGAAGTGAAGCCAGAGAAAGAACCAAGAGAACTAAAGTTAT  
GTCAGCTACCCAGACTTAATGGGCCAGAGCCATGACCCTCACAGGTCTTGTGTTAGTTGT  
ATCTGAAACTGTTATGTATCTCTCTACCTTCTGGAAAACAGGGCTGGTATTCCTACCCAG  
GAACCTCCTTTGAGCATAGAGTTAGCAACCATGCTTCTCATTCCCTTGACTCATGTCTTG  
CCAGGATGGTTAGATACACAGCATGTTGATTTGGTCACTAAAAAGAAGAAAAGGACTAAC  
AAGCTTCACTTTTATGAACAACTATTTTGAGAACATGCACAATAGTATGTTTTTATTACT  
GGTTTAATGGAGTAATGGTACTTTTATTCTTCTTGATAGAAACCTGCTTACATTTAACC  
AAGCTTCTATTATGCCTTTTTCTAACACAGACTTTCTTCACTGTCTTTCATTAAAAAGA  
AATTAATGCTCTTAAGATATATATTTTACGTAGTGCTGACAGGACCCACTCTTTCATTGA  
AAGGTGATGAAAATCAAATAAAGAATCTCTTCACATGGA

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**FIGURE 312**

MRTPGPLPVLLLLLAGAPAARPTPPTCYSRMRALSQEITRDFNLLQVSEPSEPCVRYLPR  
LYLDIHNYCVLDKLRDFVASPPCWKVAQVDSLKDKARKLYTIMNSFCRRDLVFLDDCNA  
LEYPIPVTTVLPDRQR

**Important features of the protein:**

**Signal peptide:**

amino acids 1-19

**Tyrosine kinase phosphorylation site:**

amino acids 60-69

**N-myristoylation site:**

amino acids 16-22



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**FIGURE 313**

GAGCGACGCTGTCTCTAGTCGCTGATCCCAAATGCACCGGCTCATCTTTGTCTACACTCT  
AATCTGCGCAAACCTTTTGCAGCTGTCGGGACACTTCTGCAACCCCGCAGAGCGCATCCAT  
CAAAGCTTTGCGCAACGCCAACCTCAGGCGAGATGACTTGTACCGAAGAGATGAGACCAT  
CCAGGTGAAAGGAAACGGCTACGTGCAGAGTCCTAGATTCCCGAACAGCTACCCCAGGAA  
CCTGCTCCTGACATGGCGGCTTCACTCTCAGGAGAATACACGGATACAGCTAGTGTTGA  
CAATCAGTTTGGATTAGAGGAAGCAGAAAATGATATCTGTAGGTATGATTTTGTGGAAGT  
TGAAGATATATCCGAAACCAGTACCATTATTAGAGGACGATGGTGTGGACACAAGGAAGT  
TCCTCCAAGGATAAAATCAAGAACGAACCAAATTTAAATCACATTCAAGTCCGATGACTA  
CTTTGTGGCTAAACCTGGATTCAAGATTTATTATTCTTTGCTGGAAGATTTCCAACCCGC  
AGCAGCTTCAGAGACCAACTGGGAATCTGTCACAAGCTCTATTTCAAGGGGTATCCTATAA  
CTCTCCATCAGTAACGGATCCCACTCTGATTGCGGATGCTCTGGACAAAAAATTGCAGA  
ATTTGATACAGTGGAAGATCTGCTCAAGTACTTCAATCCAGAGTCATGGCAAGAAGATCT  
TGAGAATATGTATCTGGACACCCCTCGGTATCGAGGCAGGTATACCATGACCGGAAGTC  
AAAAGTTGACCTGGATAGGCTCAATGATGATGCCAAGCGTTACAGTTGCACTCCCAGGAA  
T TACTCGGTCAATATAAGAGAAGAGCTGAAGTTGGCCAATGTGGTCTTCTTTCCACGTTG  
CCTCCTCGTGCAGCGCTGTGGAGGAAATTGTGGCTGTGGAAGTGTCAACTGGAGGTCCTG  
CACATGCAATTCAGGGAAAACCGTGAAAAAGTATCATGAGGTATTACAGTTTGAGCCTGG  
CCACATCAAGAGGAGGGGTAGAGCTAAGACCATGGCTCTAGTTGACATCCAGTTGGATCA  
CCATGAACGATGCGATTGTATCTGCAGCTCAAGACCACCTCGATAAGAGAATGTGCACAT  
CCTTACATTAAGCCTGAGAGAA

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**FIGURE 314**

MHRLIFVYTLCANFCSCRDTSATPQSASIKALRNANLRRDDLYRRDETIQVKGNGYVQS  
PRFPNSYPRNLLLTWRLHSQENTRIQLVFDNQFGLLEEAENDICRYDFVEVEDISETSTII  
RGRWCGHKEVPPRIKSRTNQIKITFKSDDYFVAKPGFKIYYSLLEDFQPAAASETNWESV  
TSSISGVSYNPSVTDPTLIADALDKKIAEFDTVEDLLKYFNPESWQEDLENMYLDTPRY  
RGRSYHDRKSKVDLDRLNDDAKRYSCTPRNYSVNIREELKLANVVFFPRCLLVQRCGGNC  
GCGTVNWRSCCNSGKTVKKYHEVLQFEPGHIKRRGRAKTMALVDIQLDHHERCDCICSS  
RPPR

**Signal peptide:**  
amino acids 1-18

**N-glycosylation site:**  
amino acids 270-274

**cAMP- and cGMP-dependent protein kinase phosphorylation site:**  
amino acids 262-266

**Tyrosine kinase phosphorylation site:**  
amino acids 256-265

**N-myristoylation sites:**  
amino acids 94-100, 186-192, 297-303, 298-304

**TonB-dependent receptor proteins signature 1:**  
amino acids 1-56

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**FIGURE 315**

CGGCTCGAGGCTCCCGCCAGGAGAAAGGAACATTCTGAGGGGAGTCTACACCCTGTGGAG  
CTCAAGATGGTCTGAGTGGGGCGCTGTGCTTCCGAATGAAGGACTCGGCATTGAAGGTG  
CTTTATCTGCATAATAACCAGCTTCTAGCTGGAGGGCTGCATGCAGGGAAGGTCATTAAA  
GGTGAAGAGATCAGCGTGGTCCCAATCGGTGGCTGGATGCCAGCCTGTCCCCCGTCATC  
CTGGGTGTCCAGGGTGGAAAGCCAGTGCCTGTATGTGGGGTGGGGCAGGAGCCGACTCTA  
ACACTAGAGCCAGTGAACATCATGGAGCTCTATCTTGGTGCCAAGGAATCCAAGAGCTTC  
ACCTTCTACCGGCGGGACATGGGGCTCACCTCCAGCTTCGAGTCGGCTGCCTACCCGGGC  
TGGTTCCTGTGCACGGTGCCTGAAGCCGATCAGCCTGTGAGCTCACCCAGCTTCCCGAG  
AATGGTGGCTGGAATGCCCCCATCACAGACTTCTACTTCCAGCAGTGTGACTAGGGCAAC  
GTGCCCCCAGAACTCCCTGGGCAGAGCCAGCTCGGGTGAGGGGTGAGTGGAGGAGACCC  
ATGGCGGACAATCACTCTCTGCTCTCAGGACCCCCACGTCTGACTTAGTGGGCACCTG  
ACCACCTTGTCTTCTGGTTCCAGTTTGGATAAATTCTGAGATTTGGAGCTCAGTCCACG  
GTCCTCCCCCACTGGATGGTGCTACTGCTGTGGAACCTTGTA AAAACCATGTGGGGTAAA  
CTGGGAATAACATGAAAAGATTTCTGTGGGGTGGGGTGGGGGAGTGGTGGGAATCATTC  
CTGCTTAATGGTAACTGACAAGTGTTACCCTGAGCCCCGAGGCCAACCCATCCCCAGTT  
GAGCCTTATAGGGTCAGTAGCTCTCCACATGAAGTCCTGTCACTCACCCTGTGCAGGAG  
AGGGAGGTGGTCATAGAGTCAGGGATCTATGGCCCTTGGCCCAGCCCCACCCCTTCCCT  
TTAATCCTGCCACTGTCAATATGCTACCTTTCCTATCTCTTCCCTCATCATCTTGTTGTGG  
GCATGAGGAGGTGGTGATGTGAGAAGAAATGGCTCGAGCTCAGAAGATAAAAGATAAGTA  
GGGTATGCTGATCCTCTTTTAAAAACCCAAGATACAATCAAAATCCCAGATGCTGGTCTC  
TATTCCTCATGAAAAGTGCTCATGACATATTGAGAAGACCTACTTACAAAGTGGCATATA  
TTGCAATTTATTTTAAATTAAGATACCTATTTATATATTTCTTTATAGAAAAAGTCTG  
GAAGAGTTTACTTCAATTGTAGCAATGTGAGGGTGGTGGCAGTATAGGTGATTTTTCTTT  
TAATTCGTGTAATTTATCTGTATTTCTAATTTTTCTACAATGAAGATGAATTCCTTGTA  
TAAAAATAAGAAAAGAAATTAATCTTGAGGTAAGCAGAGCAGACATCATCTCTGATTGTC  
CTCAGCCTCCACTTCCCCAGAGTAAATTCAAATGAATCGAGCTCTGCTGCTCTGGTTGG  
TTGTAGTAGTGATCAGGAAACAGATCTCAGCAAAGCCACTGAGGAGGAGGCTGTGCTGAG  
TTTGTGTGGCTGGAATCTCTGGGTAAGGAACCTAAAGAACAAAAATCATCTGGTAATTC  
TTCTTAGAAGGATCACAGCCCCCTGGGATTCCAAGGCATTGGATCCAGTCTCTAAGAAGGC  
TGCTGTACTGGTTGAATTGTGTCCCCCTCAAATTCACATCCTTCTTGGAATCTCAGTCTG  
TGAGTTTATTTGGAGATAAGGTCTCTGCAGATGTAGTTAGTTAAGACAAGGTCATGCTGG  
ATGAAGGTAGACCTAAATTCATATGACTGGTTTCCTTGTATGAAAAGGAGAGGACACAG  
AGACAGAGGAGACGCGGGGAAGACTATGTAAAGATGAAGGCAGAGATCGGAGTTTTGCGAG  
CCACAAGCTAAGAAACACCAAGGATTGTGGCAACCATCAGAAGCTTGGAAGAGGCAAAGA  
AGAATTCCTTCCCTAGAGGCTTTAGAGGGATAACGGCTCTGCTGAAACCTTAATCTCAGAC  
TTCCAGCCTCCTGAACGAAGAAAGAAATAAATTTCCGGCTGTTTTAAGCCACCAAGGATAAT  
TGGTTACAGCAGCTCTAGGAAACTAATACAGCTGCTAAAATGATCCCTGTCTCCTCGTGT  
TTACATTCTGTGTGTGTCCCCCTCCACAATGTACCAAAGTTGTCTTTGTGACCAATAGAA  
TATGGCAGAAGTGATGGCATGCCACTTCCAAGATTAGGTTATAAAAGACACTGCAGCTTC  
TACTTGAGCCCTCTCTCTCTGCCACCCACCGCCCCCAATCTATCTTGGCTCACTCGCTCT  
GGGGGAAGCTAGCTGCCATGCTATGAGCAGGCCTATAAAAGAGACTTACGTGGTAAAAAAT  
GAAGTCTCCTGCCCACAGCCACATTAGTGAACCTAGAAGCAGAGACTCTGTGAGATAATC  
GATGTTTGTGTTGTTTAAAGTTGCTCAGTTTTGGTCTAACTTGTTATGCAGCAATAGATAAA  
TAATATGCAGAGAAAGAG

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**FIGURE 316**

MVLSGALCFRMKDSALKVLYLHNNQLLAGGLHAGKVIKGEESVVPNRWLDASLSPVILG  
VQGSQCLSCGVGQEPTLTLEPVNIMELYLGAKESKSFTFYRRDMGLTSSFESAAYPGWF  
LCTVPEADQPVRLTQLPENGAWNAPITDFYFQQCD.

**N-myristoylation sites:**

amino acids 29-34, 30-35, 60-65, 63-68, 73-78, 91-96, 106-111

**Interleukin-1 signature:**

amino acids 111-131

**Interleukin-1 proteins:**

amino acids 8-29, 83-120, 95-134, 64-103

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**FIGURE 317**

ATGGAACTTGGACTTGGAGGCCTCTCCACGCTGTCCCACTGCCCCTGGCCTAGGCGGCAG  
CCTGCCCTGTGGCCCACCCTGGCCGCTCTGGCTCTGCTGAGCAGCGTCGCAGAGGCCTCC  
CTGGGCTCCGCGCCCCGCAGCCCTGCCCCCGCGAAGGCCCCCGCCTGTCCTGGCGTCC  
CCCGCCGGCCACCTGCCGGGGGACGCACGGCCCGCTGGTGCAGTGGAAAGAGCCCGGCGG  
CCGCCGCCGCAGCCTTCTCGGCCCCGCGCCCCCGCCGCCTGCACCCCCATCTGCTCTTCCC  
CGCGGGGGCCGCGCGGCGCGGGCTGGGGGCCCCGGGCAGCCGCGCTCGGGCAGCGGGGGCG  
CGGGGCTGCCGCCTGCGCTCGCAGCTGGTGCCGGTGCGCGCGCTCGGCCTGGGCCACCGC  
TCCGACGAGCTGGTGCGTTTCCGCTTCTGCAGCGGCTCCTGCCGCCGCGCGCGCTCTCCA  
CAGACCTCAGCCTGGCCAGCCTACTGGGCGCCGGGGCCCTGCGACCGCCCCGGGCTCC  
CGGCCCGTCAGCCAGCCCTGCTGCCGACCCACGCGCTACGAAGCGGTCTCCTTCATGGAC  
GTCAACAGCACCTGGAGAACCGTGGACCGCCTCTCCGCCACCGCCTGCGGCTGCCTGGGC  
TGA

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**FIGURE 318**

MELGLGGLSTLSHCPWRRQPALWPTLAALALLSSVAEASLGSAPRSPAPREGPPPVLAS  
PAGHLPGGRTARWCSEGRARRPPPPQPSRPAPPPPPAPPSALPRGGRAARAGGPGRARAAGA  
RGCRLRSQ LVPVRALGLGHRSDLVRFRCSESGSCRRARSPHDLASLLGAGALRPPPGS  
RPVSQPCCRPTRYEAVSFMDVNSTWRTVDRLSATACGLG

**signal sequence:**

Amino acids 1-39

**N-glycosylation site:**

Amino acids 202-206

**N-myristoylation sites:**

Amino acids 6-12;67-73;102-108;109-115;119-125

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**FIGURE 319**

GTTGCTATGTTGCCAGGCTGGTCTTGAAGTGCCCTGACCTCCTAAAGTGTTGGAACCAC  
AGACGTGAGCCACTCCACCCAGCCTAAACTTCATCTTCTTTGGATGAGATGAACACTTT  
TAACAAGAGAACAGGACTCTATATAAATCGCTGTGGGCTCACCACCTCTAAGGAGGAGCA  
CTGACTGAAGACAGAAAAATTGATGAACTGAAGAAGACATGGTCCATTATGCCTTACAAA  
CTTACACAGTGCTTTGGGAATTCCAAAGTACTCAGTGGAGAGAGGTGTTTCAGGAGCCGT  
AGAGCCAGATCGTCATCATGCTCTGCATTGTGGCTGCTGCTGGGCCTCCTTGCCCTGATGG  
ACTTGTCTGAAAGCAGCAACTGGGGATGCTATGGAAACATCCAAAGCCTGGACACCCCTG  
GAGCATCTTGTGGGATTGGAAGACGTCACGGCCTGAACTACTGTGGAGTTCTGTGCTTCTG  
AAAGGCTGGCTGAAATAGACATGCCATACCTCCTGAAATATCAACCCATGATGCAAACCA  
TTGGCCAAAAGTACTGCATGGATCCTGCCGTGATCGCTGGTGTCTTGTCCAGGAAGTCTC  
CCGGTGACAAAATTCTGGTCAACATGGGCGATAGGACTAGCATGGTGCAGGACCCTGGCT  
CTCAAGCTCCACATCCTGGATTAGTGAGTCTCAGGTTTCCCAGACAACTGAAGTTCTGA  
CTACTAGAATCAAAGAAATCCAGAGGAGGTTTCCAACCTGGACCCCTGACCAGTACCTGA  
GAGGTGGACTCTGTGCCTACAGTGGGGGTGCTGGCTATGTCCGAAGCAGCCAGGACCTGA  
GCTGTGACTTCTGCAATGATGTCTTGCACGAGCCAAGTACCTCAAGAGACATGGCTTCT  
AACATCTCAGATGAAACCCAAGACCATGATCACATATGCAGCCTCAAATGTTACACAGAT  
AAAAGTAGCCAAGGGCACCTGTAACTGGGAATCTGAGTTTGACCTAAAAGTCATTAAAT  
AACATGAATCCCATTAATAAAAAAAAAAAAAA

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**FIGURE 320**

MSALWLLLGLLALMDLSESSNWGCYGNIQSLDTPGASCGIGRRHGLNYCGVRASERLAEI  
DMPYLLKYQPMQTIGQKYCMDPAVIAGVLSRKSPGDKILVNMGDRTSMVQDPGSQAPTS  
WISESQVSQTTEVLTTRIKEIQRRFPTWTPDQYLRGGLCAYSGGAGYVRSSQDLSCDFCN  
DVLARAKYLKRHGF

**Important features of the protein:**

**Signal peptide:**

amino acids 1-19

**N-myristoylation sites:**

amino acids 23-29, 26-32, 35-41, 45-51, 50-56, 76-82, 156-162

**Amidation site:**

amino acids 40-44



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**FIGURE 321**

GCCTTATAAAGTAGCCTCTGCATCTGCCTGCCTCGGGCAGAGGAGGGCTACCCTGGGGCT  
GAGAGTTCACCTGTCTCAGGAACCACCTGAGCCACAGATCCTGTGGGCAGCGCCAGGG  
CAGCCATGGCTTGGGCAAGTAGGCTGGGCCTGCTGCTGGCACTGCTGCTGCCCCGTGGTCG  
GTGCCTCCACGCCAGGCACCGTGGTCCGACTCAACAAGGCAGCATTGAGCTACGTGTCTG  
AAATTGGGAAAGCCCCCTCTCCAGCGGGCCCTGCAGGTCACTGTCCCTCATTTCTGGACT  
GGAGTGGAGAGGGCGCTTCAGCCCACCAGGATCCGGATTCTGAATGTCCATGTGCCCCGCC  
TCCACCTGAAATTCAATTGCTGGTTTCGGAGTGCGCCTGCTGGCAGCAGCTAATTTTACTT  
TCAAGGTCTTTCGCGCCCCAGAGCCCCCTGGAGCTGACGCTGCCTGTGGAAGTGTGGCTG  
ACACCCGCGTGACCCAGAGCTCCATCAGGACCCCTGTGGTCAGCATCTCTGCCTGCTCTT  
TATTCTCGGGCCACGCCAACGAGTTTGATGGCAGTAACAGCACCTCGCACGCGCTGCTGG  
TCCTGGTGCAGAAGCACATTAAAGCTGTCTTGAGTAACAAGCTGTGCCTGAGCATCTCCA  
ACCTGGTGCAGGGTGTCAATGTCCACCTGGGCACCTTAATTGGCCTCAACCCCGTGGGTG  
CTGAGTCCCAGATCCGCTATTCCATGGTCAAGTGTGCCCACTGTCAACAGTGAATACATTT  
CCCTGGAAGTCAATGCTGTTCTCTTCTGCTGGGCAACCCCATCATCTGCCACGGATG  
CCACCCCTTTTGTGTTGCCAAGGCATGTGGGTACCGAGGGCTCCATGGCCACCGTGGGCC  
TCTCCACAGCAGCTGTTTGACTCTGCGCTCCTGCTGCTGCAGAAGGCCGGTGGCCTCAACC  
TGGACATCACAGGGCAGCTGAGGTCCGATGACAACCTGCTGAACACCTCTGCTCTGGGCC  
GGCTCATCCCGGAGGTGGCCCGCCAGTTTCCCGAGCCCATGCCTGTGGTGTCAAGGTGC  
GGCTGGGTGCCACACCTGTGGCCATGCTCCACACAAACAACGCCACCCTGCGGCTGCAGC  
CCTTCGTGGAGGTCTTGCCACAGCCTCCAACCTCGGCTTTCAGTCCCTCTTCTCCCTGG  
ATGTGGTAGTGAACCTTGAGACTCCAGCTCTCTGTGTCCAAGGTGAAGCTTCAGGGGACCA  
CGTCTGTGCTGGGGGATGTCCAGCTCACGGTGGCCTCCTCCAACGTGGGCTTCATTGATA  
CAGATCAGGTGCGCACACTGATGGGCACCGTTTTTTGAGAAGCCCCCTGCTGGACCATCTCA  
ATGCTCTCTTGCCATGGGAATTGCCCTCCCTGGTGTGGTCAACCTCCACTATGTTGCC  
CTGAGATCTTTGTCTATGAGGGCTACGTGGTGTATCCAGTGGACTCTTCTACCAGAGCT  
GAGGCAAGACCACTGGGAGGCCTGAGAGTGGGCCAGCTCGCTGCTCAGGCGAATTTCTCA  
TTTCAAGCCACTGGGGAAACTGAGGCAAAACCATAGTTCATCACCACAAAGCTGGAC  
TGCTTAGCTGGGCTGTTTTATCTTCCCTGAGTGCCTGGGTCTCCCTCCCTCACTTCTGCC  
CTTTCCCTTCTCCTCCTCTTCTCCTCCCTCTTCCCTCATCTCCCCCTCCTTCTCTGC  
CCCACCCAGGGGGGAGCAGACTGCTCCTCCAGGCTGTATAGACCTGCCCTCTTGCAATTA  
AACAACTTCTCTTGAGCTGC

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**FIGURE 322**

MAWASRLGLLLALLLPVVGASTPGTVVRLNKAALSYVSEIGKAPLQRALQVTVPHFLDWS  
GEALQPTRIRILNVHVPRLHLKFIAGFGVRLLAANFTFKVFRAPPEPLEITLPVELLADT  
RVTQSSIRTPVVSISACSLFSGHANEFDGSNSTSHALLVLVQKHIAVLSNKLCLISISNL  
VQGVNVHLGTLIGLNPVGPEsqIRYSMVSVPTVTSdyISLEVNAVLFLLGNPIILPTDAT  
PFVLPRHVGTEGSMATVGLSQQLFDSALLLQKAGALNLDITGQLRSDDNLLNTSALGRL  
IPEVARQFPPEMPVVLKVR LGATPVAMLHTN NATLRLQPFVEVLATASNSAFQSLFSLDV  
VGNLRLQLSVSKVKLQGTTSVLGDVQLTVASSNVGFIDTDQVRTLMGTVF EKPLLDHLNA  
LLAMGIALPGVVNLHYVAPEIFVYEGYVVISSGLFYQS

**Important features of the protein:****Signal peptide:**

Amino acids 1-20

**Transmembrane domain:**

Amino acids 217-236

**N-glycosylation sites:**

Amino acids 96-100;151-155;293-297;332-336

**N-myristoylation sites:**

Amino acids 8-14;149-155;189-195;249-255;252-258;283-289

**LBP / BPI / CETP family proteins:**

Amino acids 22-50; 251-287

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**FIGURE 323**

TTGAAAATCTACTCTATCAGCTGCTGTGGTTGCCACCATTCTCAGGACCCTCGCCATGAA  
AGCCCTTATGCTGCTCACCCTGTCTGTTCTGCTCTGCTGGGTCTCAGCTGACATTGCTG  
TCACTCCTGCTACAAGGTCCCTGTGCTGGGCTGTGTGGACCGGCAGTCCTGCCGCCTGGA  
GCCAGGACAGCAATGCCTGACAACACATGCATACCTTGGTAAGATGTGGGTTTTCTCCAA  
TCTGCGCTGTGGCACACCAGAAGAGCCCTGTCAGGAGGCCTTCAACCAAACCAACCGCAA  
GCTGGGTCTGACATATAACACCACCTGCTGCAACAAGGACAACCTGCAACAGCGCAGGACC  
CCGGCCCACTCCAGCCCTGGGCCTTGTCTTCCTTACCTCCTTGGCTGGCCTTGGCCTCTG  
GCTGCTGCACTGAGACTCATTCCATTGGCTGCCCCCTCCTCCACCTGCCTTGGCCTGAGC  
CTCTCTCCCTGTGTCTCTGTATCCCCTGGCTTTACAGAATCGTCTCTCCCTAGCTCCCAT  
TTCTTTAATTAAACACTGTTCCGAGTGGTCTCCTCATCCATCCTTCCCACCTCACACCCT  
TCACTCTCCTTTTTCTGGGTCCCTTCCCACCTCCTTCCAGGACCTCCATTGGCTCCTAGA  
AGGGCTCCCCACTTTGCTTCCTATACTCTGCTGTCCCCTACTTGAGGAGGGATTGGGATC  
TGGGCCTGAAATGGGGCTTCTGTGTTGTCCCCAGTGAAGGCTCCCACAAGGACCTGATGA  
CCTCACTGTACAGAGCTGACTCCCCAAACCAGGCTCCCATATGTACCCCATCCCCATA  
CTCACCTCTTTCATTTTGAGTAATAAATGTCTGAGTCTGGAAAAAAAAAAAAAAAAAAAA

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## FIGURE 324

MKALMLLTLSVLLCWVSADIRCHSCYKVPVLGCVDRQSCRLEPGQQCLTTHAYLGKMWVF  
SNLRCGTPEEPCQEAFNQTNRKLGITYNTTCCNKDNCNSAGPRPTPALGLVFLTSLAGLG  
LWLLH

**Important features of the protein:**

**Signal peptide:**

amino acids 1-18

**N-glycosylation sites:**

amino acids 77-81, 88-92

**N-myristoylation site:**

amino acids 84-90

**Ly-6 / u-PAR domain protein signature:**

amino acids 85-98

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**FIGURE 325**

ACGGGCCGCGCAGCGGCAGTGACGTAGGGTTGGCGCACGGATCCGTTGCGGCTGCAGCTCTG  
CAGTCGGGCGCGTTCCCTTCGCCGCCGCCAGGGGTAGCGGTGTAGCTGCGCAGCGTCGCGCG  
CGCTACCGCACCCAGGTTCCGGCCCCGTAGGCGTCTGGCAGCCCGGCCCATCTTCATCGAG  
CGCCATGGCCCGCAGCCTGCGGGCCGGGAGCGGCCGGGTACTGCTTGCTCCTCGGCTTGCA  
TTTGTTTTCTGCTGACCGCGGGCCCTGCCCTGGGCTGGAACGACCCTGACAGAATGTTGCT  
GCGGGATGTAAAAGCTCTTACCCTCCACTATGACCGCTATAACCACCTCCCGCAGGCTGGA  
TCCCATCCACAGTTGAAATGTGTTGGAGGCACAGCTGGTTGTGATTCTTATACCCCAA  
AGTCATACAGTGTGAGAACAAAGGCTGGGATGGGTATGATGTACAGTGGGAATGTAAGAC  
GGACTTAGATATTGCATACAAATTTGGAAAACTGTGGTGAGCTGTGAAGGCTATGAGTC  
CTCTGAAGACCAGTATGTACTAAGAGGTTCTTGTTGGCTTGGAGTATAATTTAGATTATAC  
AGAACTTGGCCTGCAGAACTGAAGGAGTCTGGAAAGCAGCACGGCTTTGCCTCTTCTC  
TGATTATTATTATAAGTGGTCCTCGGCGGATTCTGTAAACATGAGTGGATTGATTACCAT  
CGTGGTACTCCTTGGGATCGCCTTTGTAGTCTATAAGCTGTTCTTGAGTGACGGGCAGTA  
TTCTCCTCCACCGTACTCTGAGTATCCTCCATTTTCCCACCGTTACCAGAGATTACCAA  
CTCAGCAGGACCTCCTCCCCCAGGCTTTAAGTCTGAGTTCACAGGACCACAGAATACTGG  
CCATGGTGCAACTTCTGGTTTTTGGCAGTGCTTTTACAGGACAACAAGGATATGAAAATTC  
AGGACCAGGGTTCTGGACAGGCTTGGGAACCTGGTGGAATACTAGGATATTTGTTTGGCAG  
CAATAGAGCGGCAACACCCTTCTCAGACTCGTGGTACTACCCGTCCTATCCTCCCTCCTA  
CCCTGGCACGTGGAATAGGGCTTACTCACCCCTTCATGGAGGCTCGGGCAGCTATTCCGT  
ATGTTCAAACCTCAGACACGAAAACCAGAACTGCATCAGGATATGGTGGTACCAGGAGACG  
ATAAAGTAGAAAGTTGGAGTCAAACACTGGATGCAGAAATTTTGGATTTTTCATCACTTT  
CTCTTTAGAAAAAAGTACTACCTGTTAACAATTGGGAAAAGGGGATATTCAAAGTTCT  
GTGGTGTATGTCCAGTGTAGCTTTTTGTATTCTATTATTTGAGGCTAAAAGTTGATGTG  
TGACAAAATACTTATGTGTTGTATGTCAGTGTAACATGCAGATGTATATTGCAGTTTTTG  
AAAGTGATCATTACTGTGGAATGCTAAAAATACATTAATTTCTAAAACCTGTGATGCCCT  
AAGAAGCATTAGAATGAAGGTGTTGTACTAATAGAACTAAGTACAGAAAATTTCAAGTT  
TTAGGTGGTTGTAGCTGATGAGTTATTACCTCATAGAGACTATAATATTCTATTTGGTAT  
TATATTATTTGATGTTTGCTGTTCTTCAAACATTTAAATCAAGCTTTGGACTAATTATGC  
TAATTTGTGAGTTCTGATCACTTTTGAGCTCTGAAGCTTTGAATCATTCAGTGGTGGAGA  
TGGCCTTCTGGTAACTGAATATTACCTTCTGTAGGAAAAGGTGGAAAATAAGCATCTAGA  
AGGTTGTTGTGAATGACTCTGTGCTGGCAAAAATGCTTGAAACCTCTATATTTCTTTTCGT  
TCATAAGAGGTAAAGGTCAAATTTTTCAACAAAAGTCTTTTAATAACAAAAGCATGCAGT  
TCTCTGTGAAATCTCAAATATTGTTGTAATAGTCTGTTTCAATCTTAAAAAGAATCA

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**FIGURE 326**

MAAACGPGAAGYCLLLGLHLFLLTAGPALGWNDPDRMLLRDVKALTLHYDRYTTSRRLDP  
IPQLKCVGGTAGCDSYTPKVIQCQNKGDGYDVQWECKTDLDIAYKFGKTVVSCEGYESS  
EDQYVLRGSCGLEYNLDYTELG LQKLKESGKQHGFASFSDYYYKWSSADSCNMSGLITIV  
VLLGIAFVVYKFLFLSDGQYSPPPYSEYPPFSHRYQRFTNSAGPPPPGFKSEFTGPQNTGH  
GATSGFGSAFTGQQGYENSGPGFWTGLGTGGILGYLFGSNRAATPFSDSWYYPSPYPPSYP  
GTWNRAYSPLHGGSGSYSVCSNSDTKTRTASGYGGTRRR

**Signal peptide:**  
amino acids 1-30

**Transmembrane domain:**  
amino acids 171-190

**N-glycosylation site:**  
amino acids 172-176

**Glycosaminoglycan attachment sites:**  
amino acids 244-248, 259-263, 331-335

**Tyrosine kinase phosphorylation site:**  
amino acids 98-106

**N-myristoylation sites:**  
amino acids 68-74, 69-75, 131-137, 241-247, 247-253, 266-272,  
270-276, 278-284, 312-318

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**FIGURE 327**

GGCACGAGGTGGAAGGGCTTTTACAAACAGATTGCTGGCCCCACCCCCCAGAATTTCTCA  
TCAGGAGTGGGCAAGACCAATCATTTGCATTTCTGACAAGTTCCCAGGAGCTGCAGCTGC  
TGGCCCTGGAACCACACTTTGAGAACCACTGCTTTAGACCAAACACCAAAGGAAGATGCA  
GCCACCCTCCTTTACATGTCACAACGCTCAGGGTCCATGAGTACCTCAGGCTGTCCAGCT  
GAGCTCCACCTGCAGCAGCCGAGATTCCCGACTCGCTCCACCATTGGGGGCTAGGAGTGA  
AGCGTGTCACCAATGGTCAGCTCATGGCCAGCCAGGAAAGCCTCTCTGCTGTGCGTCTGTG  
CAGTTCCTTGTTCTTCCCTGGAGGACTCTTGGATCGCCTGTGATCTTGGCCAGGAGACCAG  
GTGCCTGGGTCCCTTCCCTGGAAGGGGACAAGTTACACACCCAGCCCCATTTTCCACCA  
ACTTCTACATGCCTTGGGAGAACCTTCTACATGTTGGCTGCCCCCTTCCCCTATTTTCCAGC  
AGTGCCCAAGTCCTGCTTATAAACCTGAGGCCTGCTCCCCATACCTTCCCTGTGCAAGTGC  
CAGCCGTTATTCCAGGCAGCCCAATGTTGTTGAGGCCAGATGGATTCCCTGGAAGCAGCTG  
GCCCATGGATGTGAGTCATCACAGTATTCTAGAAACAGAGAAGAGGTCTTAACCTAATGC  
GCATAGAGAAATTGTTCTCATTGTAAACATACCCCTGTCCTTAGCTGATCTAGGTGGAAG  
CCCAGCTTCATGTGCTAGGGGGCATGATAATGATAATAAAGGAATTGTATCTAGGACTAA

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## FIGURE 328

MVSSWPARKASLLCVCAVLVLPWRTLGSFVILARRPGAWVPSWKGTSYTPQPHFPTNFYM  
PWENLLHVGCPPLPLFQQCPVLLINLRPAPHTFPVQVPAVIPGSPMLLRPDGFLEAAGPWM

**Signal peptide:**  
amino acids 1-27

**cAMP- and cGMP-dependent protein kinase phosphorylation site:**  
amino acids 8-12



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**FIGURE 329**

CAAAGAGTAGTCAGTCCCTTCTTGGCTCTGCTGACACTCGAGCCCACATTCCATCACCTG  
CTCCCAATCATGCAGGTCTCCACTGCTGCCCTTGCCGTCTCCTCTGCACCATGGCTCTC  
TGCAACCAGGTCCTCTCTGCACCACTTGCTGCTGACACGCCGACCGCCTGCTGCTTCAGC  
TACACCTCCCGACAGATTCCACAGAATTTTCATAGCTGACTACTTTGAGACGAGCAGCCAG  
TGCTCCAAGCCCAGTGTTCATCTTCCTAACCAAGAGAGGCCGCGCAGGTCTGTGCTGACCCC  
AGTGAGGAGTGGGTCCAGAAATACGTCAGTGACCTGGAGCTGAGTGCCTGAGGGGTCCAG  
AAGCTTCGAGGCCAGCGACCTCAGTGGGCCAGTGGGGAGGAGCAGGAGCCTGAGCCTT  
GGGAACATGCGTGTGACCTCTACAGCTACCTCTTCTATGGACTGGTTATTGCCAAACAGC  
CACACTGTGGGACTCTTCTTAACCTAAATTTTAATTTATTTATACTATTTAGTTTTTATA  
ATTTATTTTGTATTTACAGTGTGTTTGTGATTGTTTGCTCTGAGAGTTCCCCCTGTCCC  
CTCCCCCTTCCCTCACAGTGTGTCTGGTGACAACCGAGTGGCTGTCATCGGCCTGTGTAG  
GCAGTCATGGCACCAAAGCCACCAGACTGACAAATGTGTATCAAATGCTTTTGTTCAGGG  
CTGTGATCGGCCTGGGGAAATAATAAAGATGTTCTTTTAAACGGTAAAAAA

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## FIGURE 330

MQVSTAALAVLLCTMALCNQVLSAPLAADTPTACCFSYTSRQIPQNFADYFETSSQCSK  
PSVIFLTRGRQVCADPSEEWVQKYVSDLELSA

**Signal sequence:**

1-23

**Small cytokines (intercrine/chemokine) C-C subfamily  
signature:**

1-35, 2-36, 10-44, 34-74, 50-90

**Small cytokines (intecrine/chemokine):**

24-89

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**FIGURE 331**

GGCACGAGGTGAGACTTTAAATGAAATGTCTCACAAGCTAGGTGATCCAGGTTTTGTGGT  
CTTTGCAACCCTTGTGGTCATTGTGGCCTTGATATTAATCTTCGTGGTGGGTCCTCGCCA  
TGGACAGACAAACATTCTTGTGTACATAACAATCTGCTCTGTAATCGGCGCGTTTTTCAGT  
CTCCTGTGTGAAGGGCCTGGGCATTGCTATCAAGGAGCTGTTTGCAGGGAAGCCTGTGCT  
GCGGCATCCCCCTGGCTTGGATTCTGCTGCTGAGCCTCATCGTCTGTGTGAGCACACAGAT  
TAATTACCTAAATAGGGCCCTGGATATATTCAACACTTCCATTGTGACTCCAATATATTA  
TGTATTCTTTACAACATCAGTTTTAACTTGTTCAGCTATTCTTTTTAAGGAGTGGCAAGA  
TATGCCTGTTGACGATGTCATTGGTACTTTGAGTGGCTTCTTTACAATCATTGTGGGGAT  
ATTCTTGTGTGCATGCCTTTAAAGACGTCAGCTTTAGTCTAGCAAGTCTGCCTGTGTCTTT  
TCGAAAAGACGAGAAAGCAATGAATGGCAATCTCTCTAATATGTATGAAGTTCTTAATAA  
TAATGAAGAAAGCTTAACCTGTGGAATCGAACACACACTGGTGAAAATGTCTCCCGAAG  
AAATGGAAATCTGACAGCTTTTTTAAGAAAGGTGTAATTAAAGGTAAATCTGTGATTGTTA  
TGAAGTGAATTTGAATATCATCAGAATGTGTCTGAAAAAACATTGTCCTCAAATAATGTT  
CTTTAAAGGCAATCTTTTTAAAGATTTCACTAATTTGGACCAAGAAATTACTTTTCTTGT  
ATTTAAACAAACAATGGTAGCTCACTAAAATGACCTCAGCACATGACGATTTCTATTAAC  
ATTTTATTGTTGTAGAAGTATTTTACATTTTCATCCCTTCTCCAAAAGCCGAATGCACTA  
ATGACAGTTTTAAGTCTATGAAAATGCTTTATTTTTTTCATTGGTGATGAAAGTCTGAAAT  
GTGCATTTGTTCATCCCCACTCCATCAATCCCTGACCATGTAAGGCTTTTTTATTTTAAAA  
AAACAGAGTTATCCCAATACATTATCCTGTGATTTACCTTACCTACAAAAGTGGCTCCTG  
TTTGTGTGATGATGATTGGTTTTATTTTGAATAATTTATTAAGGGAAAACCTAAGTTACT  
GAATGAAGGAACCTCTTTCCTTACAAAACAAAAAAGGGCAGAAATCACCCCAAGGAACG  
ATTTCTCAGGTTGAGATGATCACCGTGAATCCGGCTTCCTCTGAGCATTCGATGGCCTTA  
GCACCTCATCAAGCCAGCACATCCTGCCTGCTGTTGCAGCCTGGCTGGGTTTTATTCTTCA  
GTTACCCTAATCCCATGATGCCTGGAACCTTGATTACCGTTTTACATCAGCTCTTGTACT  
TTTCAGTATATTTTCATAATGAGTTATATTGTCAATTTAGACTTTGAACAGCTCTGGGAAA  
TAGAAGACTAGGTTGTTTCTTAAATTTAGCTCATGTTATAATAAAAAGTTGAAATG

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**FIGURE 332**

MSHKLGDPGFVVFATLVVIVALILIFVVGPRHGQTNILVYITICSVIGAFSVSCVKGLGI  
AIKELFAGKPVLRRHPLAWILLLSLIVCVSTQINYNRALDIFNTSIVTPIYYVFFTTSVL  
TCSAILFKEWQDMPVDDVIGTLSGFFTIIIVGIFLLHAFKDVFSFLASLPVSFRKDEKAMN  
GNLSNMYEVLNNNEESLTCGIEQHTGENVSRRNGNLTA

**Signal sequence:**

1-33

**Transmembrane domain:**

40-60, 70-90, 103-123, 139-159

**N-glycosylation site:**

103-106, 182-185, 208-211, 215-218

**N-myristoylation site:**

57-62, 140-145, 181-186, 214-219

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**FIGURE 333**

GTGATGGCGGCTGGTGATGGGGACGTGAAGCTAGGCACCCTGGGGAGTGGCAGCGAGAGC  
AGCAACGACGGCGGCAGCGAGAGTCCAGGCGACGCGGGAGCGGCAGCGGAAGGGGGAGGC  
TGGGCGGCGGCGGCGTTGGCGCTTCTGACGGGGGGCGGGGAAATGCTGCTGAACGTGGCG  
CTGGTGGCTCTGGTGCTGCTGGGGGCCCTACCGGCTGTGGGTGCGCTGGGGGCGGCGGGGT  
CTGGGGGCCGGGGCCGGGGCGGGGCGAGGAGAGCCCCGCCACCTCTCTGCCTCGCATGAAG  
AAGCGGGA<sup>1</sup>CTTCAGCTTGGAGCAGCTGCGCCAGTACGACGGCTCCCGCAACCCGCGCATC  
CTGCTCGCGGTCAATGGGAAAGTCTTCGACGTGACCAAAGGCAGCAAGTTCTACGGCCCG  
GCGGGTCCATATGGAATATTTGCTGGTAGGGATGCCTCCAGAGGACTGGCCACATTTTGC  
CTAGATAAAGATGCACTTAGAGATGAATATGATGATCTCTCAGATTTGAATGCAGTACAA  
ATGGAGAGTGTTCGAGAATGGGAAATGCAGTTTAAAGAAAAATATGATTATGTAGGCAGA  
CTCCTAAAACCAGGAGAAGAACCATCAGAATATACAGATGAAGAAGATACCAAGGATCAC  
AATAAACAGGATTGAACTTTGTAAACAACCAAAGTCAGGGGCCTTCAGAACTGCAATTCT  
TACTCCCTTTTACAGACTGTCCGGAGTCTTTGGGTTTGATTACCTGCTGCGAAAAACAT  
TCAACAAATTGTGTACAAGATAAATTAATCTCACTATGAAGATTTGAATAACTAGACATT  
ATTTATGCTGCCAAACTCATTTGTTGCAGTTGTTTGTAATGTCTAGTGGGGCTTCATCAT  
CCTGAAAAGAAGGAGACAGGGATTTTTTTAAAGAGCAAGAAAGTCACAAATATTACTTCTT  
TCCTTCCTTTTTTCCTTCTTTCCTTCTTCTTCTTCTTCTTCTTTTAAATATATTG  
AAGACAACCAGATATGTATTTGCTACTCAAGTGTACAGATCTCCTCAAGAAACATCAAGG  
G

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**FIGURE 334**

MAAGDGDVKLGTLLGSGSESSNDGGSESPGDAGAAAEGGGWAAAALALLTGGGEMLLNVAL  
VALVLLGAYRLWVRWGRRLGAGAGAGEESPATSLPRMKKRDFSLEQLROYDGSRNPRIL  
LAVNGKVFDVTKGSKFYGPAGPYGIFAGRDA SRGLATFCLDKDALRDEYDDLSDLNAVQM  
ESVREWEMQFKEKYDYVGRLLKPGEEPSEYTDEEDTKDHNKQD

**Signal sequence:**

None

**Transmembrane domain:**

45-65

**Tyrosine kinase phosphorylation site:**

202-210

**N-myristoylation site:**

11-16, 16-21, 37-42, 38-43, 79-84, 81-86, 83-88, 144-149

**Amidation site:**

75-78

**FIGURE 335**

[illegible]

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**FIGURE 336**

TGRGYCGDHESSEFGAMEEPPGATPQPYLGLLLEELRRVVAALPEGMRPDSNLYGFPWELVI  
CAAVVGFFAVLFFLWRSFRSVRSRLYVGREKKLALMLSGLIEEKSLLLEKFSLVQKEYEG  
YEVESSLKDASFEKEATEAQSLEATCEKLNRSNSELEDEILCLEKELKEEKSXHSEQDEL  
MADISKRIQSLEDESKSLKSQVAEAKMTFQIFQMNEERLKIAIKDALNENSQLOESQKQL  
LQAEVWKEQVSELNKQKVTTFEDSKVHAEQVLNDKESHIKTLTERLLKMKDWAAMLGEDI  
TDDDNLELEMNSESENGAYLDNPPKGALKKLIHAAKLNASLKTLEGERNQIYIQLSEVDK  
TKEELTEHIKNLQTTQASLOSENTHFENENQKLQOKLKVMTELYQENEMKLHRKLTVEEN  
YRLEKEEKLSKVDEKISHATEELETYRKRAKDLEEELEERTIHSYQGQIISHEKKAHDNWL  
AARNAERNLNDLRKENAHNRQKLTETELKFELLEKDPYALDVPNTAFGRGSRGPGNPLDH  
QITNERGESSCDRLTDPHRAPSDTGSLSPWDQDRMMFPPPGQSYPDALPPQQRDRFC  
SNSGRLSGPAELRSFNMPSLDKMDGSMPSMESSRNDTKDDLGNLNPDPSSLPAENEATG  
PGFVPPPLAPIRGPLFPVDARGPFLRRGPPFPFPPPPGAMFGASRDYFPPRDFPGPPPAPF  
AMRNVYPPRPGFPPYLPPRPGFFPPPHSEGRSEFPSPGLIPPSNEPATEHPEPQOET

**Signal sequence:**

None

**Transmembrane domain:**

54-74

**N-glycosylation site:**

150-153, 338-341, 636-639

**cAMP- and cGMP-dependent protein kinase phosphorylation site:**

413-416

**Tyrosine kinase phosphorylation site:**

414-421

**N-myristoylation site:**

466-417, 625-630, 697-702

**Leucine zipper pattern:**

142-163



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**FIGURE 337**

GGACTGCGGTCTCGGGCAGCAATGGCCGAGAAGCGCGACACACGGGACTCCGAAGCCCAG  
CGGCTCCCCGACTCCTTCAAGGACAGCCCCAGTAAGGGCCTTGGACCTTGC GGATGGATT  
TTGGTGGCGTTCTCATTCTTATTCACCGTTATAACTTTCCCAATCTCAATATGGATGTGC  
ATAAAGATTATAAAAGAGTATGAAAGAGCCATCATCTTTAGATTGGGTGCGATTTTACAA  
GGAGGAGCCAAAGGACCTGGTTTTGTTTTTTTATTCTGCCATGCACTGACAGCTTCATCAAA  
GTGGACATGAGAACTATTTCAATTTGATATTCTCCTCAGGAGATCTTGACAAAGGATTCA  
GTGACAATTAGCGTGGATGGTGTGGTCTATTACCGCGTTTCAAGATGCAACCCCTGGCTGTG  
GCAAATATCACCAACGCTGACTCAGCAACCCGTCTTTTGGCACAACTACTCTGAGGAAT  
GTTCTGGGCACCAAGAATCTTTCTCAGATCCTCTCTGACAGAGAAGAAATTGCACACAAC  
ATGCAGTCTACTCTGGATGATGCCACTGATGCCCTGGGGAATAAAGGTGGAGCGTGTGGAA  
ATTAAGGATGTGAAACTACCTGTGCAGCTCCAGAGAGCTATGGCTGCAGAAGCAGAAGCG  
TCCCGCGAGGCCCGCGCCAAGGTTATTGCAGCCGAAGGAGAAATGAATGCATCCAGGGCT  
CTGAAAGAAGCCTCCATGGTCATCACTGAATCTCCTGCAGCCCTTCAGCTCCGATACCTG  
CAGACACTGACCACCATTGCTGCTGAGAAAACTCAACAATTGTCTTCCCTCTGCCCATA  
GATATGCTGCAAGGAATCATAGGGGCAAAACACAGCCATCTAGGCTAGTGTAGAGATGAG  
CGCTAGCCTTCCAAGCATGAAGTCGGGGACCAAATTAGCCTTTAACTCATAAAGAGAGGG  
TAGGGCTTTTCTTTTCCATATGTCAATTGTGGTGTTC CAGAATGTATAGCAGTTATAA  
AAATAGGTGAAAGAATTGTTAGCTTGTAATACTGAGAGATTGGTGATTATATAAGGTA  
ATCTGTTAGTCTTAAATAGTTAAAGTTTGTATTTTATAGATTATTATGTAGTAGGTTAG  
ATCCCTCTTGTTTTGA CTCTCACTGACTCATTCTGAACCCCTAAGCACCCAGGCCACAG  
GCAAGAACCTGGGCTGTA ACTGCCACCTGACACCGCTGACTGGCTAAATGCTTTGCAGAA  
AGTGATGACCTTACACCACAACCAGCTTCTCCAGGTCATATGTGCCTTACCTCCAGAAGT  
CTTTTTTTTTTTTTTTTTCTGAGATGGAGTTTCACTCTTGTGTC CAGGCTGGAGTGCAA  
TAGCATGATCTCGGCTCACTGCAACCTCCGCCTCCTGGGTTCAAGAGATTCTCCTGCCTC  
AGCCTCCCCAGTAGCTGGGATTACAGGCTCATGCCACCATGCCCAGCTAATTTTGTATT  
ATTATTATTGTTTTTTAGTAGAGACGGGGTTTACCATTGTTGGCCAGGCTAGTCACGAAC  
TCCTAACCTCAGGTGATCCACCCACCTCTGCCTCCAAAGTGCTGGATTACAGGCTGAGCT  
ACCACCCTGGTTTGGAGAGTCTTAATTAATTGAAATTTCCCTAATGTTTCAATTTATTTCT  
AAATCCAGCCGTGTTT CAGAATAATCCTTACTTGAGAGTAGCCATTTTCTTGTGTACTTG  
TCAGAACTAGAGGAAATAGCCAAGACTAATGAAAAACATTACTCTAACCCCTTAAAGACT  
TTTAAATTCATACTAGAGTGGTCATTTTAAAAATACATCCATGTTTTAACTTATTTTGA  
GCCTTCTTTTATGAGTAAATGATTCTCCTTGTCTGTCTTTCAAACCAGCTAAATATT  
TGTCACAAAAGTGACTTTTTTCTCACTGTTGCCTATTTTCATATATCAGGTTTTAAATAG  
TTTTAATTTTTTAATAAAATTTTTCTCTACGTTCTATATGCAATTGTTATATATCTATTT  
GAATAGCTGAAGGACTAAAATACTTTTTTAAGAGATAACTTCAGGAAACCATTATATTTT  
ACTATCTGCATGCTGTAACTGTGGTACACTGTGAAATATGTTGATTACAAACCCATTCA  
TTACATAGTATAAGGAATTCACAGTATATTGACTATATAGTGTCTAATGACTGGGCAGAT  
ACTGTCAACTTACAATATCTATATAGAGAGGCTTTAAACTTACCTTACTCATTCTCTATG  
ATGTATGACTTGATGCTGAAAGAGGAAGCTGGTCAGCTCCTCATGGACAACAAATCTTA  
GTCTATAATATTAGGAGACATCTCTAGTTTTTGCAAATGTCTGTGAATCTGAGCAACCTGG  
ACTTCTGCTTACTGGCCAGAAAGCTGGCGGGTGACATTTGTAACATTTCCCTCTTTGAGAC  
TCTGAGTTACCTAGAGAAGTCTAAGCATAACAGCTTTCTTTCCCAGCACGAGCCTTTAT  
AGCTCTCTTTAGCTCAACCACTCTGTCCATCCAGCCAATGGATGTCTTCCCTGTACCCA  
ATTCAAGCTTATTTTAGGGAAGCCTTGAAACTACCATGTATCTGGCTCTAGCTGAGTTAT  
TGAGGATTGAGCCAGTGCAACGTTAAACTCAGTGCACCTTACATTTGATTTAAATGATGGT  
TTTATCTGTTGTGTGAAGTGGTTACCCCTTGAGGACCAGGAGCCTCCATATCCTGACTGA  
AAACCTTTTTCTGAGACTTAGAGTAACAGTACTTTTGGTTCCTTGAGTTCTCCTGTCTCCA  
GATACCTAAATGACCTTGACTTTTTCTGCCTTGTGAATTCGTAGTCCAATCAGCTGAAATT  
AAATCACTTGGGAGGGACGCATAGAAGGAGCTCTAGGAACACAGTGCCAGTGCAAGATT  
TCTCCAGGTGGCCTCCCTTTCCAACAATGTACATAATAAAGTGTATGCACTTTCACT

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**FIGURE 338**

MAEKRDTRDSEAQRLPDSFKDSPSKGLGPCGWILVAFSFLFTVITFPISIWMCIKIIKEY  
ERAIIFRLGRILQGGAKGPGLFFILPCTDSFIKVD MRTISFDIPPQEILTKDSVTISVDG  
VVYYRVQNATLAVANITNADSATRLLAQTTLRNVLGTKNLSQILSDREEIAHNMQSTLDD  
ATDAWGIKVERVEIKDVKLPVQLQRAMAAEAEASREARAKVIAAEGEMNASRALKEASMV  
ITESPAALQLRYLQTLTTIAAEKNSTIVFPLPIDMLQGIIGAKHSHLG

Signal sequence:

1-45

Transmembrane domain:

None

N-glycosylation site:

128-131, 135-138, 159-162, 229-232, 264-267

cAMP- and cGMP-dependent protein kinase phosphorylation  
site:

4-7

N-myristoylation site:

26-31, 278-283, 281-286

SPFH domain/Band 7 family:

39-230

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**FIGURE 339**

TCTAGAGCCCTCTCCCAACATGGCGGCCTCAGCAAAAAGAAGAATAAGAAGGGGAAGAC  
TATCTCCCTAACAGACTTTCTGGCTGAGGATGGGGGTACTGGTGGAGGAAGCACCTATGT  
TTCCAAACCAGTCAGCTGGGCTGATGAAACGGATGACCTGGAAGGAGATGTTTCGACCAC  
TTGGCACAGTAACGATGACGATGTGTATAGGGCGCCTCCAATTGACCGTTCCATCCTTCC  
CACTGCTCCACGGGCTGCTCGGGAACCCAATATCGACCGGAGCCGTCTTCCCAAATCGCC  
ACCCTACACTGCTTTTCTAGGAAACCTACCCTATGATGTTACAGAAGAGTCAATTAAGGA  
ATTCTTTCGAGGATTAAATATCAGTGCAGTGCCTTTACCACGTGAACCCAGCAATCCAGA  
GAGGTGAAAGGTTTTGGTTATGCTGAATTTGAGGACCTGGATTCCCTGCTCAGTGCCCT  
GAGTCTCAATGAAGAGTCTCTAGGTAACAGGAGAATTCGAGTGGACGTTGCTGATCAAGC  
ACAGGATAAAGACAGGGATGATCGTTCTTTTGGCCGTGATAGAAATCGGGATTCTGACAA  
AACAGATACAGACTGGAGGGCTCGTCTTGCTACAGACAGCTTTGATGACTACCCACCTAG  
AAGAGGTGATGATAGCTTTGGAGACAAGTATCGAGATCGTTATGATTGAGACCGGTATCG  
GGATGGGTATCGGGATGGGTATCGGGATGGCCACGCCGGGATATGGATCGATATGGTGG  
CCGGGATCGCTATGATGACCGAGGCAGCAGAGACTATGATAGAGGCTATGATTCCCGGAT  
AGGCAGTGGCAGAAGAGCATTTGGCAGTGGGTATCGCAGGGATGATGACTACAGAGGAGG  
CGGGGACCGCTATGAAGACCGATATGACAGACGGGATGATCGGTGCTGGAGCTCCAGAGA  
TGATTACTCTCGGGATGATTATAGGCGTGATGATAGAGGTCCCCCCCCAAGACCCAACT  
GAATCTAAAGCCTCGGAGTACTCCTGAAGAAGATGATTCTCTGCTAGTACCTCCCAGTC  
CACTCGAGCTGCTTCTATCTTTGGAGGGGCAAAGCCTGTTGACACAGCTGCTAGAGAAAG  
AGAAGTAGAAGAACGGCTACAGAAGGAACAAGAGAAGTTGCAGCGTCAGTGGAAATGAGCC  
AAAAGTAGAACGACGGCCTCGGGAGAGACACCCAAGCTGGCGAAGTGAAGAACTCAGGA  
ACGGGAACGGTGCAGGACAGGAAGTGAGTCATCACAACTGGGACCTCCACCACATCTAG  
CAGAAATGCACGAAGGAGAGAGAGTGAGAAGTCTCTAGAAAATGAAACACTCAATAAGGA  
GGAAGATTGCCACTCTCCAACCTTCTAAACCTCCCAAACCTGATCAGCCCCCTAAAGGTAAT  
GCCAGCCCCCTCCACCAAAGGAGAATGCTTGGGTGAAGCGAAGTTCTAACCCTCCTGCTCG  
ATCTCAGAGCTCAGACACAGAGCAGCAGTCCCCTACAAGTGGTGGGGGAAAAGTAGCTCC  
AGCTCAACCATCTGAGGAAGGACCAGGAAGGAAAGATGAAAATAAAGTAGATGGGATGAA  
TGCCCCAAAAGGCCAACTGGGAACTCTAGCCGTGGTCCAGGAGACGGAGGGGAACAGAGA  
CCACTGGAAGGAGTCAGATAGGAAAGATGGCAAAAAGGATCAAGACTCCAGATCTGCACC  
TGAGCCAAAAGAAACCTGAGGAAAATCCAGCTTCTAAGTTCAAGTTCTGCAAGCAAGTATGC  
TGCTCTCTCTGTTGATGGTGAAGATGAAAATGAGGGAGAAGATTATGCCGAATAGACCTC  
TACATCCTGTGCTTTTCTCCTAGTTTCTCTCCACCCTGGAACATTCGAGAGCAAATCAAA  
ACCTCTATCCAGACAAGACAAAATAAACTCAACATCTCCTGAAGACCTTTCTTACCTTT  
TTTTAAAAACAAAAXTGAAATTATTTTGCATGCTGCTGCAGCCTTTAAAGTATTGAAGT  
AACTGGAGAATTGCCAATACAGCCAGAGAGAAAGGGACTACAGCTTTTTTAGAGGAAAAGT  
TGTTGGTGCGTTATGTCACCATGCAGTTGCCAGTGTGATTAGTGCCTAGGGGTCTCATTTA  
GCAGAAATGGTAATGACAGTGATATAATGCCTGGAACCTGGTTGGGCAGTAGGGGAGGGA  
GGTAGAAGGAAAAGTGTGAGATTTCTACCTTTTAGTTTTCATCCTATTGTGGCATATATG  
AATTCTCAAACATTATCTGAATAAATTTTCCACTCTTGGAAGGTAGATTTAGCCTCAAG  
TTGTTCTAGTCTCCAGGAGGCTGCCAGCCCCCTCCTCTTATTTAATTCTGAGTTTTGGGGG  
CCAGCCTAGAGGGAATTCCTTTTTTTTTTTTTTTTAAACCCCCAGGGGGGTAGTTGGGAGT  
GAGACTATAGGCCATAAAGAAATGGGACTGCATTGGACCAAAATAAATGGGAAAATCGTGG  
TTTGAAAAGAAGCTTTTGGGAAGTGATGAGTCATTTTGCACCAGGTAATAGGGGAAAATT  
GTGTGACCTCCAGCAAACACATGAATGGTTATTTCTTGAGCCGGAAGCACTTGGGGGTCT  
GTGGTAATTCCCAGTGTTTTCTGTGTCTAGTTTTTACCCTTTCTAAACACTGTCCTTTTT  
GAAAGTTTTGAATATATCCACATTCTATTGAAACCTTGAAACTAAAAATTTAGACTCTTA  
TCGTCACTCTTAAGTTCTTCATGCTACTCTTAACCTCCCAAAAAGCAGTATCTAAGTCACA  
TACATGATGTCTTGGGCATTTTCTGAGCCATGGAGAAGTCTGAAAGGAAGAATCGCTGCT  
TTTCTCAAGCAAATCGGTTTTCTTGATGTCTTTTGGTTCTCCTTGCTGCTCCTGATGCTT

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GGACCCCTTTTATTGATCAGAGTGCTCTAGAATAATGGATGGTCTTGGATGATGGATAAA  
TAGGGACAGGGACAGTTAAATTGGGAGCCTTTCTTACAACCTTGATGGGATTTTTCCCCC  
CAAGTTTCCTTCTCCACTGAAATGCCACACTAATGCTTGTTGGATTGATGAGGTGGCCAG  
ACCAATGTGTTGTTTTGTTGTTGTTTTTTTTTTAAGCTTCCCTTGAGAGAATAAATGGTA  
ATGGAGAGAATCATTTAACAAGGTCTGCTTCTTGCAACACAGTAGCTAAACTTGCC  
TGCTTTTATATGCATTTTTGTAGGGATCAGCTTGGTAGACAGTATTAGCGGAGAAACACC  
TTGATCTTGGTTTGCAAGCCCTTCTCCCATCAGTCCTAGATTAGGCCCTGTTTCAGCCATG  
CAGGGGTGTTGGTTTATGCGTGCTGCAGCAGTGGGCATAATGAATATAATTTACCCAGTG  
GACAAAGGTGTGTACCAAGTGAATTTAAATAATTGGTGTGGATTGGCCAGTAGCTAAGAA  
GTGGGCTTTTAAAGAGTATTGAAGATTGAAAGGGTTTTTCTTCTTTTTTAAAAAGAAA  
AACAACTATTGATTGTAGATAATGAAAAGCTAGGGTTTGCCCTCTTCATGTCTACTCTC  
CTTCCAAATAGTTATATCCAAACTGTTTTTCCCTCTCCCTACCTTGTCCCCCTATTA  
AAATAGAAACAGGGATTGATTAATGTCCCGCTCCTGAATACATGTAAAAATTTGTACAAAA  
ATATCTTCTATGAAAATGATTTGTAATCTGTAGACTTATTACCTGGGAGATGTCTTGATG  
TAAATCCCATCCTTTGGGTTGTGGGTTTTTTGTTTTTCTCCAAATAAATCTGATCTTTAA  
AGTTAAAAAAAAAAAAAAAACTCTAGAGTCGAGGAATTC

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**FIGURE 340**

MAASAKKKNKKGKTI SLTDFLAEDGGTGGGSTYVSKPVSWADETDDLEGDVSTTWHSNDD  
DVYRAPPIDRSILPTAPRAAREPNIDRSRLPKSPPYTAFLGNLPYDVTEESIKEFFRGLN  
ISAVRLPREPSNPERLKGFGYAEFEDLDSLLSALSLSNEESLGNRRIRVDVADQAQDKDRD  
DRSFGRDRNRDSKTDTDWRARPATDSFDDYPPRRGDDSFQDKYRDRYDSRYRDGYRDG  
YRDGPRRDMDRYGGDRYDDRGSRDYDRGYDSRIGSGRRAFGSGYRRDDDYRGGGDRYED  
RYDRRDDRWSRSSRDDYSRDDYRRDDRGPPQRPKLNKPRSTPEEDDSSASTSQSTRAASI  
FGGAKPVDTAAREREVEERLQKEQEKLRQWNEPKLERRPRERHPSWRSEETQERERSRT  
GSESSQTGTSTTSSRNARRRESEKSLNETLNKEEDCHSPTSKPPKPDQPLKVMPPPPK  
ENAWVKRSSNPPARSQSSDTEQQSPTSGGGKVAPAPQSEEGPGRKDENVKVDGMNAPKGQT  
GNSSRGPGDGGNRDHWKESDRKDGKKDQDSRSAPEPKKPEENPASKFSSASKYAALSVDG  
EDENEGEDYAE

**Signal Sequence:**

None

**Transmembrane domain:**

None

**N-glycosylation site:**

120-123, 448-451, 542-545

**Glycosaminoglycan attachment site:**

507-510

**cAMP- and cGMP-dependent protein kinase phosphorylation site:**

439-442, 486-489

**Tyrosine kinase phosphorylation site:**

225-233, 264-270

**N-myristoylation site:**

25-30, 26-31, 28-33, 118-123, 421-426, 428-433, 538-543

**Amidation site:**

276-279, 522-525, 563-566

**Cell attachment sequence:**

215-217

**Eukaryotic putative RNA-binding region RNP-1 signature:**

137-144

**RNA recognition motif:**

98-168

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**FIGURE 341**

GCGTGGACACCACCTCAGCCCACTGAGCAGGAGTCAACAGCACGAAGACCAAGCGCAAAGC  
GACCCCTGCCCTCCATCCTGACTGCTCCTCCTAAGAGAGATGGCACCGGCCAGAGCAGGA  
TTCTGCCCCCTTCTGCTGCTTCTGCTGCTGGGGCTGTGGGTGGCAGAGATCCCAGTCAGT  
GCCAAGCCCAAGGGCATGACCTCATCACAGTGGTTTAAAATTCAGCACATGCAGCCCAGC  
CCTCAAGCATGCAACTCAGCCATGAAAAACATTAACAAGCACACAAAACGGTGCAAAGAC  
CTCAACACCTTCCTGCACGAGCCTTCTCCAGTGTGGCCGCCACCTGCCAGACCCCCAAA  
ATAGCCTGCAAGAATGGCGATAAAAACTGCCACCAGAGCCACGGGCCCCGTGTCCCTGACC  
ATGTGTAAGCTCACCTCAGGGAAGTATCCGAACTGCAGGTACAAAGAGAAGCGACAGAAC  
AAGTCTTACGTAGTGGCCTGTAAGCCTCCCCAGAAAAAGGACTCTCAGCAATTCCACCTG  
GTTCCCTGTACACTTGGACAGAGTCCTTTAGGTTTCCAGACTGGCTTGCTCTTTGGCTGAC  
CTTCAATTCCCTCTCCAGGACTCCGCACCACTCCCCTACACCCAGAGCATTCTCTTCCCC  
TCATCTCTTGGGGCTGTTCCCTGGTTTCAGCCTCTGCTGGGAGGCTGAAGCTGACACTCTGG  
TGAGCTGAGCTCTAGAGGGATGGCTTTTCATCTTTTGTGTGCTGTTTTCCCAGATGCTTA  
TCCCCAAGAAACAGCAAGCTCAGGTCTGTGGGTTCCCTGGTCTATGCCATTGCACATGTC  
TCCCCTGCCCCCTGGCATTAGGGCAGCATGACAAGGAGAGGAAATAAATGGAAAGGGGGC  
AAA  
AAA

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**FIGURE 342**

MAPARAGFCPLLLLLLLGLWVAEIPVSAKPKGMTSSQWFKIQHMQPSPQACNSAMKNINK  
HTKRCKDLNTFLHEPFSSVAATCQTPKIACKNGDKNCHQSHGPVSLTMCKLTSGKYPNCR  
YKEKRQNKSYVVACKPPQKKDSQQFHLVPVHLDRVL

**Important features of the protein****Signal peptide:**

1-22

**Transmembrane domain:**

none

**N-glycosylation site:**

127-131

**cAMP- and cGMP-dependent protein kinase phosphorylation  
site:**

139-143

**N-myristoylation site:**

18-24, 32-38

**Pancreatic ribonuclease family signature:**

65-72

**Pancreatic ribonuclease family proteins:**

49-93

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## FIGURE 343

GCATTTGCCACTGGTTGCAGATCAGGCGGACGAGGAGCCGGGAAGGCAGAGCCATGTGGC  
TGCCCCCTGCTCTGCTCCTTCTCAGCCTCTCAGGCTGTTTCTCCATCCAAGGCCAGAGT  
CTGTGAGAGCCCCAGAGCAGGGGTCCCTGACGGTTCAATGCCACTATAAGCAAGGATGGG  
AGACCTACATTAAGTGGTGGTGCCGAGGGGTGCGCTGGGATACATGCAAGATCCTCATTG  
AAACCAGAGGGTCGGAGCAAGGAGAGAAGAGTGACCGTGTGTCCATCAAGGACAATCAGA  
AAGACCGCACGTTCACTGTGACCATGGAGGGGCTCAGGCGAGATGACGCAGATGTTTACT  
GGTGTGGGATTGAAAGAAGAGGACCTGACCTTGGGACTCAAGTGAAAGTGATCGTTGACC  
CAGAGGGAGCGGCTTCCACAACAGCAAGCTCACCTACCAACAGCAATATGGCAGTGTTCA  
TCGGCTCCCACAAGAGGAACCACTACATGCTCCTGGTATTTGTGAAGGTGCCCATCTTGC  
TCATCTTGGTCACTGCCATCCTCTGGTTGAAGGGGTCTCAGAGGGTCCCTGAGGAGCCAG  
GGGAACAGCCTATCTACATGAACTTCTCCGAACCTCTGACTAAAGACATGGCCACTTAGA  
GAGATGGATCTGCAGAGCCTTCCCTGCCCTGGCCACGTTTCCAGAAGAGACTCGGGCTGTG  
GAAGGAACATCTACGAGTCCTCGGGATGCAGTGACTGAGATAGGGGGCCCTGGGCCTCCGC  
CCTGGCCTTGGAGCTGGTGGGCACCTCCCTGTTCTGCACAGCTCAGGGACTTAGCCAGGT  
CCTCTCCTGAGCCACCATCACCTCCTGGGGTGCCAGCACCTGTTCTCTTGGTCAGGAGCT  
GTAGAGATGGAGCTCAAGCACTGGACGACTCTGTCCCCACTGCTGGAATAACTCGGGCAC  
AGAGCATGGGACCAAAGTACAGAAAGAGGTTGGGGGAGACCCCCCAGCCCTAGACTTCC  
ATCATTCGGGAGACCAACTCAACACCGTCTTTGCCTGAGAACCTGATATATCCGTGTTTT  
TAAATTTTTTTTTTTCTAGCAAAGTTGGGTTTTAATGACTTATGTTCATAGGAAACCTCT  
CTGATCCCACACACAAGGAGGGTGATTCTGGGATGAGTTCCTGGTTCTAGGGCATGAGGG  
GCTGGATGGACCCTGTCCCCAGGGAGGACATGGCTCTGAGTCCACAGGGCTGAGGAGGCA  
ATGGGAACCTCCCTGGCCCCGGCCGGTGCTTGTCTCCCCCTCCCACCTCTTCTCTCTCC  
TAGCTCCCCAAGCTCCCTGCCTATTCCCCCACCTCCGAGGGGCTGCAGCTTGGGAGCCTC  
CTCAGCATGACAGCTTGGGTCTCTCCCCAAAAGAGCCTGTGAGGCCTCAAGAACCACCT  
CCAGGTGGGGAGGGCAGTAACGAAAACCATCGCAGGAAATGGCACCCCTCCCTTTTCGGTG  
ATGTTGAAATCATGTTACTAATGAAAACGTCTCTAGGGAAGTGGTTCTGTCTCTCTCACAG  
GCTTCACCCACGGCGATGAGGCCCTTGAATGTGGTCACTTTGTGCTGTATGGTTGAGGGA  
CCCTCACACCAAAGGGACCTTCCCATGTGAGATGTGCTCCCGCCCCCACCTGCCACACAAG  
CAAACACACCACACATGTTCCGCATGTTGCCCTTTGAACACCCATGAGGACGCCCTCCAAC  
CTGCTCTTGGTTCTAATAGGGAGTACTGACTGTCAGCAGTGGATAAAGGAGAGGGGACCC  
TCTGGTCCCTAGCATGGCACCCAGAGCCTCCCTCTTCTTGTCTTCTCAGCCAAAGAGAAA  
CTTTCTCTGACTTTGAACTGAATTTAGGTCTCTGGCCAATGATGGGCCTGAAAATTCCAT  
AATGGCCAGAGAGGAGAGTTCGAGCCCGGCTAAGATCCCCTGAGTCATTCTGTGAGGGAC  
CAAGACCCACAGTCCACCAGCCCCAGGGCCCTACCTCCTGGAATGCTTTCTTGGATCCAG  
CTTCCCGAAGATCCGACCAGACCCAGGGAGGACGGCACCGCTCCGCGGGAGGGGAAAGCCA  
AAGCATGGTGCTTCACCAGCTGGACTCAGGGGCGAGGGGACATGGGCGCTTGTCAACGTG  
ATGTCATTCTTTCCACCGTTTCTTCTGTTGATATTCAATGAATCCGTCAATCTCTCT  
GGGAAA



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**FIGURE 344**

MWLPPALLLLSLSGCFSIQGPESVRAPEQGS�TVQCHYKQGWETIYIKWWCRGVRWDTCKI  
LIETRGSEQGEKSDRVSİKDNQKDRTFTVTMEGLRRDDADVWCGİERRGPDŁGTQVKVI  
VDPEGAASTTASSPTNSNMAVFIGSHKRNHYMLLVFVKVPİLLİLVTAILWLKGSQRVPE  
EPGEQPIYMFSEPLTKDMAT

**Important features of the protein:**

**Signal peptide:**

Amino acids 1-17

**Transmembrane domain:**

Amino acids 151-170

**N-glycosylation site:**

Amino acids 190-194

**Tyrosine kinase phosphorylation site:**

Amino acids 95-103

**N-myristoylation sites:**

Amino acids 66-72; 125-131

**Prokaryotic membrane lipoprotein lipid attachment site:**

Amino acids 5-16

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**FIGURE 345**

CTGAGCTCCCGGGCTCCGGCAGCGCGCTGGCGGGGCGCCGCATTGCACACTCTGGGGGCG  
CCGCAGTGTTCGTGGGATGGGGCAGCGGGCTGCAGCTGGCGGCCGGAATCCGCGCGCAGC  
CCGGGTGCAAGTTCTCTCCTGTTGCCCTGAGTGCCCACTCCAGGCCCTCTGTATGAGTG  
ACACTTCAGTCTGCCATGGAACCTGGCCCTGCTCTGGCCTGGCTCCTGCTCCTGAGCCTG  
CTGGCGGATTGTCTGAAAGCTGCTCAGTCCCGAGACTTCACAGTGAAAGACATTATCTAC  
CTCCATCCTTCAACCACACCATATCCTGGTGGATTAAATGTTTCACCTGTGAAAAGGCA  
GCAGACAATTATGAGTGCAACCGATGGGCTCCAGACATCTACTGCCCTCGAGAGACCAGA  
TACTGCTACACTCAGCACACAATGGAAGTCACAGGAAACAGTATCTCAGTCACCAAACGC  
TGTGTCCCACTGGAAGAGTGCTTATCCACTGGCTGCAGAGACTCCGAGCATGAAGGCCAC  
AAGGTCTGCACTTCTTGTTGTGAAGGAAATATCTGTAACCTTGCCACTGCCCCGAAATGAA  
ACTGATGCCACATTTGCCACGACGTCACCTATAAATCAGACAAATGGGCACCCACGCTGT  
ATGTCAGTGATAGTGTCTGCTTGTGGTTGTGGTTAGGGCTCATGTTATAGTGGCTCAGT  
GGCTCCATGTGTTAATAGCGATCCATGGGGATCTCGATGGTCCACAGACCTGCATGAGTC  
ATTGGCCTGACAGTAATTACACATGTGAGACACAACACTCTTGGAGGTCATCACAGCCAA  
GCATTGCCACTTACCATGAGGAATAAATGTTGCTTCATTGTAGCCATTTTGAGTCTAACC  
GAGACTCATCAAAGCCTTCTGTCTAGTACAGCCCAAGTTCATACCATAAACGTTTGT  
CATTCCAAGAAGTAGTTCTGCATTTATCGAGATCTGGGGTTCTTAATTTGGAAGAATACA  
TGCATGAGATGCAGTAGGTCCTGAGACTGTAAGATATTAGGAGTATGTTATAGGGGCATG  
TATAGATGTGGGCTTTTCAGGAGAAAAGTAACCATTTGGTTTAAATATAATCATGAGTTCA  
TTTGTAGCTTTAGAATTTTAAACATTGACTCCAACTGAATGGACTATTTCTTGGAAA  
TTCTGACTGAGTCCCTGGAAGAGTAGTAATTCCAACAATTCCAGCCATTTGTTCAATTAA  
TTTTCCCAACATTCCTCTCCAGTGCTGGGAATCACATTTCTCTGTTCTGTGCAGAAGA  
CAAAAAGGCAATCATAAAAGTTTGTATATTTGTGGGGGTGCCTGGAGGAGGATTTTCT  
CAACTTAATGGAGCCACTGTCCATAAAGTGGCTGTTATCCCTTCATATAATTGGTGAGAT  
CAGCCTTCTCCTTGACTTGGCACCTAATTATGCTTCATGAGATCCTAGATTCCACCTGAG  
TCAATTGTGTCCAGAGCCCCAAACCAGGATGGAGTTGTTTTCCCCAGATATGGGGTTCTA  
TTCAGCCATAGATAATCTAGACAGAGGATTTCAGAATGAAAGGAAAAATGTGTGGAGATT  
AGTCCTAGTTTCACTCTGAGGGCCGACTAAGTGGCTCAGCCAGCTTCTTACTCCATCTGCA  
GTTTCATACTGCCAAAGAGCTCCCACTTCCAAATCCCCAGTGACTTTATGGAGAAGATTCT  
GCATTAAATTGTCTTTCGAATGATGGGGAAGCAAGGCATAATATGCGATGATGAGGAGAA  
AGTAGACCAGTGAGGTGATTGCAAGACTAACAAGGAGACTCAATGGGAAGTTTTTCTTTC  
TTTTAGATATTGCTTTTGAAGTAGATGGTAAATTTTTGTTCATCCTTCTTGATTTTTTG  
TACCCCAAGTTACAATTTTCTTCTTCTTGTAAATAATTTAAACAGTATTTATTTTTGT  
AAGGCATAACTAGAACTAAATATATTCTAAAAAATTCATTATTCTGAACAAAGTGATC  
AAATTAGAATACATATTTTCAACAGTGGTAGAGCTTTTAATATATGTTTATTGAAAGTT  
ATCTATAATACTTGCACCAGTGTTGAAAAAAGTTAACATGTAGGCAAGAGCAATATGTTT  
GTCTCAAGGATTTTTCCATGGTTTCTCAGTGATGGTGTCTGGAATTATTGAGGTGGTG  
ACCATCACTGGTCTAAGTTTGTGTGCAGGGTTTTTCAGACGTGTTTTTGTGAACTTGGA  
GAACCATGGCTAATAAAGAGGACAGTGTTGTGAGGGTCCATCTGCCCTCCATAGAAAAAT  
GTCTCTGGCTCATAAAATGAGACTCCCTCAGGGACTAAATATGAACTGACAGCAGTAACT  
CTGATACAGAATAATCTAAATTGCATCAAATGGCCTTAATTCAGAGTTTGTTAGGCTTAT  
CAGTATGTTGCTTTTAATTGGGGTGGGAAAGTAGAGGGAGAGAAAGCAAGACATTTATTA  
AGCACCTCGTATGTGCCAGGCACTATGCTAAGCACTTTACATAAGTTAGGATTAATCCCT  
GCAAGAATCCTATAAAGAATGTTACTAGCATTTACACTTCCCAAATGAAGGTACCAAAGC  
TCAAACGCAATGTTGTGAAGCTGTTTCTTTCAGATTTAGGTTATGTGGGATGATGTGGGA  
TTGAAGAGGAAAGAAAGGTGGGATTATCCCCCTAGGAAGACTTTCAGGCCTGACTTCATA  
GGAATTCATCCATCTTATCATGTGGAGTTTATCTCACCTGCTGTTGCAGGATGCTATTT  
GCATGTGTCCCAGGTGATGTTTTTCTTTGGGGAGTAGGGGTTTGGCTTCTCATTCAT

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CCCTCTGCTAAAAGAGGAGATAGTTGATGTTCATCTAAAGATGCTATAAGACAATGAAAGTTTGTGTGTAC  
ATACCTACAAGTACCATTTTTGTGCATGATTACACTCCACTGACATCTTCCAAGTACTAC  
ATGTGATTGAATAAGAAACAAGAAAGTGACCACACCAAAGCCTCCCTGGCTGGTGTACAG  
GGATCAGGTCCACAGTGGTGCAGATTCAACCACCACCCAGGGAGTGCTTGCAGACTCTGC  
ATAGATGTTGCTGCATGCGTCCCATGTGCCTGTCAGAATGGCAGTGTTTAATTCTCTTGA  
AAGAAAGTTATTTGCTCACTATCCCCAGCCTCAAGGAAGCCAAGGAAGAGTCATTACATG  
GAAGGTCCGGGACTGGTCAGCCACTCTGACTTTTCTACCACATTAAATTCTCCATTACAT  
CTCACTATTGGTAATGGCTTAAGTGTAAGAGCCATGATGTGTATATTAAGCTATGTGCC  
ACATATTTATTTTGTAGACTCTCCACAGCATTGATGTCAATATGGGATTAATGCCTAAACT  
TTGTAAATATTGTACAGTTTGTAAATCAATGAATAAAGGTTTTGAGTGTAACAAAAAAAAA  
AAAAAA

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**FIGURE 346**

MEPGPALAWLLLLSLADCLKAAQSRDFTVKDIIYLHPSTTPYPGGFKCFTCEKAADNYE  
CNRWAPDIYCPRETRYCYTQHTMEVTGNSISVTKRCVPLEECLSTGCRDSEHEGHKVCTS  
CCEGNICNLPLPRNETDATFATTSPINQTNHPRCMSVIVSCLWLWLGLML

**Important features of the protein:****Signal peptide:**

1-22

**Transmembrane domain:**

None

**N-glycosylation site:**

134-138, 147-151

**N-myristoylation site:**

45-51, 87-93, 106-112, 124-130

**Ly-6 / u-PAR domain protein:**

115-128

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**FIGURE 347**

GATCAAGCGCCTTCCTTTCCCTTCCTCTCCCTACTTGGCCTTTGCCCTAAGCCAAGACCT  
GGCCATCAGCCTGGCTGCAGGGGCTGCAGAGCCAGCTGCACTTTTTCAGGTATGGGGGA  
GGGCCAGGCACCATGAAGCCAGTGTGGGTCGCCACCCTTCTGTGGATGCTACTGCTGGTG  
CCCAGGCTGGGGGCCCGCCGGAAGGGGTCCCCAGAAGAGGCCTCCTTCTACTATGGAACC  
TTCCCTCTTGGCTTCTCCTGGGGCGTGGGCAGTTCTGCCTACCAGACGGAGGGCGCCTGG  
GACCAGGACGGGAAAGGGCCTAGCATCTGGGACGTCTTCACACACAGTGGGAAGGGGAAA  
GTGCTTGGGAATGAGACGGCAGATGTAGCCTGTGACGGCTACTACAAGGTCCAGGAGGAC  
ATCATTCTGCTGAGGGAACTGCACGTCAACCACTACCGATTCTCCCTGTCTTGGCCCCGG  
CTCCTGCCCACAGGCATCCGAGCCGAGCAGGTGAACAAGAAGGGAATCGAATTCTACAGT  
GATCTTATCGATGCCCTTCTGAGCAGCAACATCACTCCCATCGTGACCTTGCACCACTGG  
GATCTGCCACAGCTGCTCCAGGTCAAATACGGTGGGTGGCAGAATGTGAGCATGGCCAAC  
TACTTCAGAGACTACGCCAACCTGTGCTTTGAGGCCTTTGGGGACCGTGTGAAGCACTGG  
ATCACGTTTCAGTGATCCTCGGGCAATGGCAGAAAAAGGCTATGAGACGGGGCCACCATGCG  
CCGGGCCTGAAGCTCCGCGGCACCGGCCTGTACAAGGCAGCACACCACATCATTAAGGCC  
CACGCCAAAACCTGGCATTCTTATAACACCACGTGGCGCAGCAAGCAGCAAGGTCTGGTG  
GGAATTTCACTGAACTGTGACTGGGGGGAACCTGTGGACATTAGTAACCCCAAGGACCTA  
GAGGCTGCCGAGAGATACCTACAGTTCTGTCTGGGCTGGTTTGCCAACCCCATTTATGCC  
GGTGACTACCCCAAGTCATGAAGGACTACATTGGAAGAAAGAGTGCAGAGCAAGGCCTG  
GAGATGTGAGGTTACCGGTGTTCTCACTCCAGGAGAAGAGCTACATTAAAGGCACATCC  
GATTTCTTGGGATTAGGTCATTTTACTACTCGGTACATCACGGAAAGGAACTACCCCTCC  
CGCCAGGGGCCCAGCTACCAGAACGATCGTGACTTGATAGAGCTGGTTGACCCAACTGG  
CCAGATCTGGGGTCTAAATGGCTATATTCTGTGCCATGGGGATTTAGGAGGCTCCTTAAC  
TTTGCTCAGACTCAATACGGTGATCCTCCCATATATGTGATGGAAAATGGAGCATCTCAA  
AAATTCCACTGTACTCAATTATGTGATGAGTGGAGAATTCAATACCTTAAAGGATACATA  
AATGAAATGCTAAAAGCTATAAAAGATGGTGCTAATATAAAGGGGTATACTTCCTGGTCT  
CTGTTGGATAAGTTTGAATGGGAGAAAGGATACTCAGATAGATATGGATTCTACTATGTT  
GAATTTAACGACAGAAATAAGCCTCGCTATCCAAAGGCTTCAGTTCAATATTACAAGAAG  
ATTATCATTGCCAATGGGTTTCCCAATCCAAGAGAGGTGGAAAGTTGGTACCTCAAAGCT  
TTGGAAACTTGCTCTATCAACAATCAGATGCTTGCTGCAGAGCCTTTGCTAAGTCACATG  
CAAATGGTTACGGAGATCGTGGTACCCACTGTCTGCTCCCTCTGTGTCCTCATCACTGCT  
GTTCTACTAATGCTCCTCCTGAGGAGGCAGAGCTGAGACAGGATTATCAATTTTGGAGCT  
TCATAAGAGAATCTTCAGGATCTTCCTCCCTTTTCTGCTTTGAGGGTTTCCATACATTGC  
TGTTTTTCAGGTTCTACAATAATTACCTTTTTTTCTCTTTCTCTTTTGGCTTGTGCTGGG  
ATTTAAGAATTAGAAAATAAAAATAAGCAGAAATTA

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**FIGURE 348**

MKPVWVATLLWMLLLVPRLLGAARKGSPEEASFYYGTFPLGFSWGVGSSAYQTEGAWDQDG  
KGPSIWDVFTHSGKGKVLGNETADVACDGYKQEDIILLRELHVNHYRFSLSWPRLPT  
GIRAEQVNKKGIEFYSDLIDALLSSNITPIVTLHHWDLPLLQVKYGGWQNVSMANYFRD  
YANLCFEAFGDRVKHWITFSDPRMAEKGYETGHHAPGLKLRGTGLYKAAHHIIKAHAKT  
WHSYNTTWRSKQQGLVGISLNCDWGEPVDISNPKDLEAAERYLQFCLGWFPANPIYAGDYP  
QVMKDYIGRKSAEQGLEMSRLPVFSLQEKSYIKGTSDFLGLGHFTTRYITERNYPSRQGP  
SYQNDRLIELVDPNWPDLGSKWLYSVPWGFRLLNFAQTQYGDPPYVMENGASQKFHC  
TQLCDEWRIQYLKGYINEMLKAIKDGANIKGYTSWSLLDKFEWEKGYSdryGFYYVEFND  
RNKPRYPKASVQYYKKIIANGFPNPREVESWYLKALETCSINNQMLAAEPLLSHMQMVT  
EIVVPTVCSLCVLITAVLLMLLLRRQS

**Important features:****Signal peptide:**

amino acids 1-21

**Transmembrane domain:**

amino acids 541-558

**N-glycosylation sites:**

amino acids 80-84,171-175,245-249

**Glycosaminoglycan attachment site:**

amino acids 72-76

**cAMP- and cGMP-dependent protein kinase phosphorylation sites:**

amino acids 23-27,564-568

**Tyrosine kinase phosphorylation sites:**

amino acids 203-211,347-355,460-468,507-514

**N-myristoylation sites:**

amino acids 44-50,79-85,167-173,225-231,257-263,315-321

**Amidation site:**

amino acids 307-311

**Glycosyl hydrolases family 1 active site:**

amino acids 407-416

**Glycosyl hydrolases family 1 N-terminal signature:**

amino acids 41-56

**Motif name Glycosyl hydrolases family:**

amino acids 37- 67

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**FIGURE 349**

CGCAAAGCCGCCCTCGGGGCGCTCATGGCGGGACGCCTCCTGGGAAAGGCTTTAGCCGCG  
GTGTCTCTCTCTGGCCTTGGCCTCTGTGACTATCAGGTCCTCGCGCTGCCGCGGCATC  
CAGGCGTTTCAAGAACTCGTTTTTCATCTTCTTGTTTTTCATCTTAATACCAACGTCATGTCT  
GGTTCTAATGGTTTCAAAGAAAATTCTCACAATAAGGCTCGGACGTCTCCTTACCCAGGT  
TCAAAGTTGAACGAAGCCAGGTTCTAATGAGAAAGTGGGCTGGCTTGTGAGTGGCAA  
GACTATAAGCCTGTGGAATACACTGCAGTCTCTGTCTTGGCTGGACCCAGGTGGGCAGAT  
CCTCAGATCAGTGAAAGTAATTTTTCTCCCAAGTTTAAAGAAAGGATGGGCATGTTGAG  
AGAAAGAGCAAGAATGGCCTGTATGAGATTGAAAATGGAAGACCGAGAAATCCTGCAGGA  
CGGACTGGACTGGTGGGCCGGGGGCTTTTGGGGCGATGGGGCCCAAATCACGCTGCAGAT  
CCCATTATAACCAGATGGAAAAGGGATAGCAGTGGAAATAAAATCATGCATCCTGTTTCT  
GGGAAGCATATCTTACAATTTGTTGCAATAAAAAGGAAAGACTGTGGAGAATGGGCAATC  
CCAGGGGGGATGGTGGATCCAGGAGAGAAGATTAGTGCCACACTGAAAAGAGAATTTGGT  
GAGGAAGCTCTCAACTCCTTACAGAAAACCAGTGCTGAGAAGAGAGAAATAGAGGAAAAG  
TTGCACAACTCTTCAGCCAAGACCACCTAGTGATATATAAGGGATATGTTGATGATCCT  
CGAAACACTGATAATGCATGGATGGAGACAGAAGCTGTGAACTACCATGACGAAACAGGT  
GAGATAATGGATAATCTTATGCTAGAAGCTGGAGATGATGCTGGAAAAGTGAAATGGGTG  
GACATCAATGATAAACTGAAGCTTTATGCCAGTCACTCTCAATTTCATCAAACCTTGTGGCT  
GAGAAACGAGATGCACACTGGAGCGAGGACTCTGAAGCTGACTGCCATGCGTTGTAGCTG  
ATGGTCTCCGTGTAAGCCAAAGGCCACAGAGGAGCATATACTGAAAAGAAGGCAGTATC  
ACAGAATTTATACTATAAAAAGGGCAGGGTAGGCCACTTGGCCTATTTACTTTCAAACA  
ATTTGCATTTAGAGTGTTTCGCATCAGAATAACATGAGTAAGATGAACTGGAACACAAAA  
TTTTCAGCTCTTTGGTCAAAGGAATATAAGTAATCATATTTTGTATGTATTTCGATTTAA  
GCATGGCTTAAATTAAATTAAACAACCTAATGCTCTTTGAAGAATCATAATCAGAATAAA  
GATAAATTCTTGATCAGCTATA

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**FIGURE 350**

MAGRLLGKALAAVSLSLALASVTIRSSRCRGIQAFRNSFSSSWFHLNTNVMMSGNSNGSKEN  
SHNKARTSPYPGSKVERSQVPNEKVGWLVWQDYKPVEYTAVSVLAGPRWADPQISESNF  
SPKFNEKDGHVERKSKNGLYEIEGRPRNPAGRTGLVGRGLLGRWGNHAAADPIITRWKR  
DSSGNKIMHPVSGKHILQFVAIKRKDCGEWAIPGGMVDPGEKISATLKREFGEEALNSLQ  
KTSAEKREIEEKLHKLFSQDHLVIYKGYVDDPRNTDNAWMETEAVNYHDETGEIMDNMLL  
EAGDDAGKVKWVDINDKLKLYASHSQFIKLVAEKRDAHWESEADCHAL

**Important features of the protein:****Signal peptide:**

1-20

**Transmembrane domain:**

None

**N-glycosylation site:**

55-59

**cAMP- and cGMP-dependent protein kinase phosphorylation site:**

179-183

**N-myristoylation site:**

53-59, 56-62

**mutT domain signature:**

215-235



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**FIGURE 351**

CCTCTGTCTGTGCTCCCATCCCAGGGAGTATAGGTGGAGCCTCCAGAGCCCATGGACAGG  
GCATGCTGGGGCTGGGCCAGCCCCAGCGGTGTCTCTAAGGCACCCCTGGGATCCCCACTG  
AGCTGGCCTACTTCAGACAGCCAGGGCCCCACCCCTCTGGCCCCCTTAGTGTCCAGCTCGT  
GGCCCCCTTGGCATTTCACAAGACGCCAAGATGGAGATTCCCATGGGGACCCAGGGCTGC  
TTCTCAAAGAGCCTCCTGCTCTCAGCCTCAATCCTGGTCCTCTGGATGCTCCAAGGCTCC  
CAGGCAGCTCTCTACATCCAGAAGATTCCAGAGCAGCCTCAAAAGAACCAGGACCTTCTC  
CTGTCAGTCCAGGGTGTCCCAGACACCTTCAGGACTTCAACTGGTACCTGGGGGAGGAG  
ACGTACGGAGGCACGAGGCTATTTACCTACATCCCTGGGATACAACGGCCTCAGAGGGAT  
GGCAGTGCCATGGGACAGCGAGACATCGTGGGCTTCCCCAATGGTTCATGCTGCTGCGC  
CGCGCCCAGCCTACAGACAGTGGCACCTACCAAGTAGCCATTACCATCAACTCTGAATGG  
ACTATGAAGGCCAAGACTGAGGTCCAGGTAGCTGAAAAGAATAAGGAGCTGCCCAGTACA  
CACCTGCCCCACCAACGCTGGGATCCTGGCGGCCACCATCATTGGATCTCTTGCTGCCGGG  
GCCCTTCTCATCAGCTGCATTGCCATCTCTCTGGTGACAAGGAACCTGGAGGGGCCAGAGC  
CACAGACTGCCTGCTCCGAGGGGCCAGGGATCTCTGTCCATCTTGTGCTCGGCTGTATCC  
CCAGTGCCCTCAGTGACGCCCAGCACATGGATGGCGACCACAGAGAAGCCAGAATTGGGC  
CCTGCTCATGATGCTGGTGACAACAACATCTATGAAGTGATGCCCTCTCCAGTCCCTCTG  
GTGTCCCCCATCAGTGACACAAGGTCCATAAACCCAGCCCCGGCCCCCTGCCACACCCCCA  
CACCTGCAGGCGGAGCCAGAGAACCACCAGTACCAGCAGGACCTGCTAAACCCCGACCCCT  
GCCCCCTACTGCCAGCTGGTGCCAACTTCCTGATGGGTCTCTGGGCCAGGCCAGCCAGGGA  
GAAGACAAGGCCCCAGCCCTCCTCTGGGAGCCTCACACCTGAGACCAGCAGGACAAGGCC  
ATTGGGGGCTGTGGGGCCGATGAGGTGGACTCAGCCAAAGACTCAGCAGCACATGGGGCA  
GGTGTCTTGGCAGGGGGACAGGAGACTGTAACAGGCCCAGGTCTTGTGTCAGCCCCCTGAA  
TGCACGCCCCGCTTCGGTCTGTTCCCTTCAAGCAAGCTGGCCTGGGCCATGTGCCTGTGAA  
AGGCAGGCTCTGGCCCCCTTCCATGCCAAAGTCCCCCAAGATCTGGATATCTGGGGACAA  
GATGGTGGCCTCAGGCCTGCCTCCCAGGCAGTTGGCTGGGCTCCCAACTGTCTGTCTCA  
ATGCCCTACCCCAACTCCACTAGTGACCCTCAGAGTCTTCTCCCCCTTAGGACAAGGCAGA  
CACCCACCATGCGGGCCTCAGGTGGCAGAGAGGCCCAGCCTCACAGGCCTGTGGCCCCA  
CACACCAGTCCCAGCAAGGTGACCACGGCTGCTGGACCCCTTCCCTGTTTCAGGCAGGCCC  
AGCCCCCTCTCAGAACCTGCTGCCAGCTGCTGGTCTTGGCCCCCACCCTGAATCTTACTGA  
GTCCCTCTGGGCAGCAGCTCCCTTCTCCACCCACCCACAGCACCCTGCCAAATGTGGCC  
TCAGCTTGTCTCTCCCTTCCCCAACTATGCATTCATTAGCAATAAATGAGCCTTTGCT  
GCA

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**FIGURE 352**

MEIPMGTQGCFSKSLLLSASILVLWMLQGSQAALYIQKIPEQPQKNQDLLLSVQGVPDF  
QDFNWYLGEETYGGTRLFTYIPGIQRPQRDGSAMGQDIVGFPNGSMLLRRAPTDSTY  
QVAITINSEWTMAKTEVQVAEKNKELPSTHLPSTNAGILAATTIGSLAAGALLISCIAYL  
LVTRNWRGQSHRLPAPRGQGSLSILCSAVSPVPSVTPSTWMATTEKPELGPAGDAGDNNI  
YEVMPSPVLLVSPISDTRSINPARPLPTPPHLQAEPEHNYQQDLLNPDPAPYCQLVPTS

**Important features of the protein:****Signal peptide:**

Amino acids 1-32

**Transmembrane domain:**

Amino acids 159-178

**N-glycosylation site:**

Amino acids 104-108

**N-myristoylation sites:**

Amino acids 6-12; 29-35; 55-61; 91-97; 157-163; 165-171

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**FIGURE 353**

CTTCAGAACAGGTTCTCCTTCCCCAGTCACCAGTTGCTCGAGTTAGAATTGTCTGCAATG  
GCCGCCCTGCAGAAATCTGTGAGCTCTTTCCTTATGGGGACCCTGGCCACCAGCTGCCTC  
CTTCTCTTGGCCCTCTTGGTACAGGGAGGAGCAGCTGCGCCCATCAGCTCCCAGTGCAGG  
CTTGACAAGTCCAACCTCCAGCAGCCCTATATCACCAACCGCACCTTCATGCTGGCTAAG  
GAGGCTAGCTTGGCTGATAACAACACAGACGTTCGTCTCATTGGGGAGAACTGTTCCAC  
GGAGTCAGTATGAGTGAGCGCTGCTATCTGATGAAGCAGGTGCTGAACTTCACCCTTGAA  
GAAGTGCTGTTCCCTCAATCTGATAGGTTCCAGCCTTATATGCAGGAGGTGGTGCCCTTC  
CTGGCCAGGCTCAGCAACAGGCTAAGCACATGTCATATTGAAGGTGATGACCTGCATATC  
CAGAGGAATGTGCAAAAGCTGAAGGACACAGTGAAAAAGCTTGGAGAGAGTGGAGAGATC  
AAAGCAATTGGAGAACTGGATTTGCTGTTTATGTCTCTGAGAAATGCCTGCATTTGACCA  
GAGCAAAGCTGAAAAATGAATAACTAACCCCTTTCCCTGCTAGAAATAACAATTAGATG  
CCCCAAAGCGATTTTTTTTAAACCAAAGGAAGATGGGAAGCCAAACTCCATCATGATGGG  
TGGATTCCAAATGAACCCCTGCGTTAGTTACAAAGGAAACCAATGCCACTTTTGTTTATA  
AGACCAGAAGGTAGACTTTCTAAGCATAGATATTTATTGATAACATTTTCATTGTAAGTGG  
TGTTCTATACACAGAAAACAATTTATTTTTTAAATAATTGTCTTTTCCATAAAAAAGAT  
TACTTTCCATTCCTTTAGGGGAAAAAACCCCTAAATAGCTTCATGTTTCCATAATCAGTA  
CTTTATATTTATAAATGTATTTATTATTATTATAAGACTGCATTTTATTTATATCATTTT  
ATTAATATGGATTTATTTATAGAAACATCATTCGATATTGCTACTTGAGTGTAAGGCTAA  
TATTGATATTTATGACAATAATTATAGAGCTATAACATGTTTATTTGACCTCAATAAACA  
CTTGGATATCCC

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**FIGURE 354**

MAALQKSVSSFLMGTLATSCLLLLALLVQGGAAAPISSHCRLDKSNFQQPYITNRTFMLA  
KEASLADNNTDVRLIGEKLFHGVSMSERCYLMKQVLNFTLEEVLPQSDRFQPYMQEVVP  
FLARLSNRLSTCHIEGDDLHIQRNVQKLKDTVKKLGESGEIKAIGELDLLFMSLRNACI

**Important features of the protein:**

**Signal peptide:**

amino acids 1-33

**N-glycosylation sites:**

amino acids 54-58, 68-72, 97-101

**N-myristoylation sites:**

amino acids 14-20, 82-88

**Prokaryotic membrane lipoprotein lipid attachment site:**

amino acids 10-21

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**FIGURE 355**

TGGCCTACTGGAAAAAAAAAAAAAAAAAAAAAGTCACCCGGGCCCCGCGGTGGCCACAA  
CATGGCTGCGGCGCCGGGGCTGCTCTTCTGGCTGTTCGTGCTGGGGGCGCTCTGGTGGGT  
CCCGGGCCAGTCGGATCTCAGCCACGGACGGCGTTTCTCGGACCTCAAAGTGTCGGGGA  
CGAAGAGTGCAGCATGTTAATGTACCGTGGGAAAGCTCTTGAAGACTTCACGGGCCCTGA  
TTGTCGTTTTGTGAATTTTAAAAAAGGTGACGATGTATATGTCTACTACAACTGGCAGG  
GGGATCCCTTGAACCTTGGGGCTGGAAGTGTTGAACACAGTTTTTGGATATTTTCCAAAAGA  
TTTGATCAAGGTACTTCATAAATACACGGAAGAAGAGCTACATATTCCAGCAGATGAGAC  
AGACTTTGTCTGCTTTGAAGGAGGAAGAGATGATTTTAAATAGTTATAATGTAGAAGAGCT  
TTTAGGATCTTTGGAACTGGAGGACTCTGTACCTGAAGAGTCGAAGAAAGCTGAAGAAGT  
TTCTCAGCACAGAGAGAAATCTCCTGAGGAGTCTCGGGGGCGTGAACTTGACCCTGTGCC  
TGAGCCCGAGGCATTTCAGAGCTGATTTCAGAGGATGGAGAAGGTGCTTCTCAGAGAGCAC  
CGAGGGGCTGCAGGGACAGCCCTCAGCTCAGGAGAGCCACCCTCACACCAGCGGTCTCTGC  
GGCTAACGCTCAGGGAGTGCAGTCTTCGTTGGACACTTTTGAAGAAATTCTGCACGATAA  
ATTGAAAGTGCCGGGAAGCGAAAGCAGAACTGGCAATAGTTCTCCTGCCTCGGTGGAGCG  
GGAGAAGACAGATGCTTACAAAGTCCTGAAAACAGAAATGAGTCAGAGAGGAAGTGGACA  
GTGCGTTATTTCATTACAGCAAAGGATTTTCGTTGGCATCAAAATCTAAGTTTGTTTTACAA  
AGATTGTTTTTTAGTACTAAGCTGCCTTGGCAGTTTGCATTTTTTGAGCCAAACAAAAATAT  
ATTATTTTCCCTTCTAAGTAAAAAAAAAAAAAAAAAAAAA

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**FIGURE 356**

MAAAPGLLFWL FVLGALWWVPGQSDLSHGRRFSDLKVCGDEEC SMLMYRGKALEDFTGPD,  
CRFVNFKKGDDVYVYYKLAGGSLELWAGSVEHSFGYFPKDLIKVLHKEYTEELHIPADET  
DFVCFEGGRDDFNSYNVEELLGSLELEDSVPEESKKAEEVSQHREKSPPEESRGRELD PVP  
EPEAFRA DSE DGE GAFSE STEGLQGQPSAQESH PHTSGPAANAQGVQSSLDTFEEILHDK  
LKVPGESERTGNSSPASVEREKTDAYKVLKTEMSQRGSGQCVIHYSKGFRWHQNL SLFYK  
DCF

**Important features of the protein:**

**Signal peptide:**

amino acids 1-22

**N-glycosylation site:**

amino acids 294-298

**cAMP- and cGMP-dependent protein kinase phosphorylation site:**

amino acids 30-34

**Tyrosine kinase phosphorylation site:**

amino acids 67-76

**N-myristoylation sites:**

amino acids 205-211, 225-231, 277-283

**Amidation site:**

amino acids 28-32

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**FIGURE 357**

[illegible]

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**FIGURE 358**

MEAPGPRALRTALCGGCCCLLLCAQLAVAGKGARGFGRGALIRLNIWPAVQGACKQLEVC  
EHCVEGDRARNLSSCMWEQCRPEEPGHCVAQSEVVKEGCSIYNRSEACPAHHHPTYPEPK  
TVTTGSPVPPEAHSPGFDGASFIGGVVLVLSLQAVAFFVLHFLKAKDSTYQTL

**Important features of the protein:****Signal peptide:**

1-29

**Transmembrane domain:**

141-160

**N-glycosylation site:**

71-75, 103-107

**Tyrosine kinase phosphorylation site:**

164-171

**N-myristoylation site:**

15-21



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**FIGURE 359**

TTCCAGTCAGAGTTAAGTTAAAACAGAAAAAAGGAAGATGGCAAGAATATTGTTACTTTT  
CCTCCCGGGTCTTGTGGCTGTATGTGCTGTGCATGGAATATTTATGGACCGTCTAGCTTC  
CAAGAAGCTCTGTGCAGATGATGAGTGTGTCTATACTATTTCTCTGGCTAGTGCTCAAGA  
AGATTATAATGCCCCGACTGTAGATTCATTAACGTTAAAAAAGGGCAGCAGATCTATGT  
GTACTCAAAGCTGGTAAAAGAAAATGGAGCTGGAGAATTTGGGCTGGCAGTGTTTATGG  
TGATGGCCAGGACGAGATGGGAGTCGTGGGTATTTCCCCAGGAACTTGGTCAAGGAACA  
GCGTGTGTACCAGGAAGCTACCAAGGAAGTTCCCACCACGGATATTGACTTCTTCTGCGA  
GTAAATAAATTAGTTAAAACGCAAATAGAAAGAAAACACCAAAAATAAAGAAAAGAGCAA  
AAGTGGCCAAAAAATGCATGTCTGTAATTTTGGACTGACGT

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## FIGURE 360

MARILLLLFLPGLVAVCAVHGIFMDRLASKKLCADDECVYTISLASAQEDYNAPDCRFINV  
KKGQQIYVYSKLVKENGAGEFWAGSVYGDGQDEMGVVGYFPRNLVKEQRVYQEATKEVPT  
TDIDFFCE

Important features of the protein:

Signal peptide:

1-14

Transmembrane domain:

None

N-myristoylation site:

84-90

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**FIGURE 361**

GGCACGAGCCACCACTTACAACCACACAGCCTATCCAGAAACATGAAGATAAGAAATGCT  
TGTGCTGTCCTTATTGAAGTACTCCTGTTTATACTTGAAGGAGTTACAGGAGCTCGAAAA  
ATTTCAACTTCTCAGGCCCTGGCTCATGGCCGTGCAATCCCAAGTGTGATGGCAGAACT  
TACAACCCCTCAGAGGAGTGTTGTGTTTATGACACCATCCTGCCCTTTAAGCGGATTAAC  
CTCTGTGGCCCTAGCTGCACCTACAGGCCCTGCTTTGAGCTCTGCTGTCTGAGTCCTAT  
AGCCCCAAGAAGAAATTTATTGTCAAGCTTAAAGTTCATGGAGAGAGATCCCATTGCAGT  
TCATCCCCTATCTCCAGGAAGTGTAAAAGCAACAAGATTTTTTCATGGAGAAGATATTGAA  
GACAACCAACTTTCTCTTAGGAAAAAAGTGGTGACCAGCCTTGAGAGTCTGCTTTCTTC  
CTGCAAGCACCAGTTCCTGAATGTTCTTACTTGAAGAATGGATACCTGAAGCATTGGGGT  
GCAGTGATATATGTGTCTCATTACAATGCTCCTTTGGATATTGTTTTCTAAGCATGTGT  
TGGAATGTTCCCCCATAACTTTCTAAAATTATCCTATTTCAATGCAACTAAAGATAAATG  
TATTCAGCCAGAGTCCACAGAGAAGGCAAGTTATGCAAGGCAGGCATGGGGCCCTCACA  
AAATTTCAAGCTGTGCGACTTATGTAGTAATTTTCTACAAACAATCCCTCCTGGATATCC  
AGGAGGCTCCAGACCTGAATAAAAACCACATGTCTGTCTAGAAAAAGGGAATGAATCAAG  
ATCCACAGGACCTTTTCAAGATTTTAGAAGCAGCAAACCTATGGCTGAGAGAAAAGACTCT  
CTGACCAGGCAAATTGTTCTGCAGTATTCTCCGGGCGTGTAGCTCCCCTGAGTAGTCGCC  
AGGCTGGTCTTGGCTTTGTAATAATACAGCTGCCTTTGAGTCCTCCCTACCCCTGTTAGTA  
ACCCCTTGCTGCACTGTTGTCCTTACAACCGAAATAAACTGATTAGTTG

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## FIGURE 362

MKIRNACAVLIEVLLFILEGVTGARKISTFSGPGSWPCNPKCDGRTYNPSEECCVHDTIL  
PFKRINLCGPSCTYRPCFELCCPESYSPKKKFIVKLKVHGERSHCSSSPISRNCKSNKIF  
HGEDIEDNQLSLRKKSGDQP

Important features of the protein:

Signal peptide:

1-23

Transmembrane domain:

None

Glycosaminoglycan attachment site:

31-35

N-myristoylation site:

20-26, 34-40

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**FIGURE 363**

ACACTGGCCAAACAAAAACGAAAGCACTCCGTGCTGGAAGTAGGAGGAGAGTCAGGACTC  
CCAGGACAGAGAGTGCACAACTACCCAGCACAGCCCCCTCCGCCCCCTCTGGAGGCTGA  
AGAGGGATTCCAGCCCCCTGCCACCCACAGACACGGGCTGACTGGGGTGTCTGCCCCCTT  
GGGGGGGGCAGCACAGGGCCTCAGGCCTGGGTGCCACCTGGCACCTAGAAGATGCCTGT  
GCCCTGGTTCTTGCTGTCTTGGCACTGGGCCGAAGCCCAGTGGTCTTTCTCTGGAGAG  
GCTTGTGGGGCCTCAGGACGCTACCCACTGCTCTCCGGGCCTCTCCTGCCGCCTCTGGGA  
CAGTGACATACTCTGCCTGCCTGGGGACATCGTGCCCTGCTCCGGGCCCCGTGCTGGCGCC  
TACGCACCTGCAGACAGAGCTGGTGCTGAGGTGCCAGAAGGAGACCGACTGTGACCTCTG  
TCTGCGTGTGGCTGTCCACTTGGCCGTGCATGGGCACCTGGGAAGAGCCTGAAGATGAGGA  
AAAGTTTGGAGGAGCAGCTGACTCAGGGGTGGAGGAGCCTAGGAATGCCTCTCTCCAGGC  
CCAAGTCGTGCTCTCCTTCCAGGCCTACCTACTGCCCGCTGCGTCTGCTGGAGGTGCA  
AGTGCCTGCTGCCCTTGTGCAGTTTGGTCACTGTGTGGGCTCTGTGGTATATGACTGCTT  
CGAGGCTGCCCTAGGGAGTGAGGTACGAATCTGGTCTTATACTCAGCCAGGTACGAGAA  
GGAACCTCAACCACACACAGCAGCTGCCTGCCCTGCCCTGGCTCAACGTGTGACGAGATGG  
TGACAACGTGCATCTGGTTCTGAATGTCTCTGAGGAGCAGCACTTCGGCCTCTCCCTGTA  
CTGGAATCAGGTCCAGGGCCCCCAAAACCCCGGTGGCACAAAAACCTGACTGGACCGCA  
GATCATTACCTTGAACCACACAGACCTGGTTCCCTGCCTCTGTATTACAGGTGTGGCCTCT  
GGAACCTGACTCCGTTAGGACGAACATCTGCCCTTTCAGGGAGGACCCCGCGCACACCA  
GAACCTCTGGCAAGCCGCCCCGACTGCGACTGCTGACCCTGCAGAGCTGGCTGCTGGACGC  
ACCGTGCTCGCTGCCCGCAGAAGCGGCACTGTGCTGGCGGGCTCCGGGTGGGGACCCCTG  
CCAGCCACTGGTCCCACCGCTTTCCTGGGAGAACGTCACTGTGGACAAGGTTCTCGAGTT  
CCCATTGCTGAAAGGCCACCCTAACCTCTGTGTTTCAGGTGAACAGCTCGGAGAAGCTGCA  
GCTGCAGGAGTGCTTGTGGGCTGACTCCCTGGGGCCTCTCAAAGACGATGTGCTACTGTT  
GGAGACACGAGGCCCCCAGGACAACAGATCCCTCTGTGCCTTGGAAACCCAGTGGCTGTAC  
TTCACTACCCAGCAAAGCCTCCACGAGGGCAGCTCGCCTTGGAGAGTACTTACTACAAGA  
CCTGCAGTCAGGCCAGTGCTCTGCAGCTATGGGACGATGACTTGGGAGCGCTATGGGCCTG  
CCCCATGGACAAATACATCCACAAGCGCTGGGCCCTCGTGTGGCTGGCCTGCCTACTCTT  
TGCCGCTGCGCTTTCCTCATCCTCCTTCTCAAAAAGGATCACGCGAAAGGGTGGCTGAG  
GCTCTTGAAACAGGACGTCCGCTCGGGGGCGGCCGCCAGGGGCGCGCGGCTCTGCTCCT  
CTACTCAGCCGATGACTCGGGTTTCGAGCGCCTGGTGGGCGCCCTGGCGTCCGCCCTGTG  
CCAGCTGCCGCTGCGCGTGGCCGTAGACCTGTGGAGCCGTCTGTAACCTGAGCGCGCAGGG  
GCCCGTGGCTTGGTTTCACGCGCAGCGGCCAGACCCTGCAGGAGGGCGCGGTGGTGGT  
CTTGCTCTTCTCTCCCGGTGCGGTGGCGCTGTGCAGCGAGTGGCTACAGGATGGGGTGT  
CGGGCCCGGGGCGCACGGCCCGCACGACGCTTCCGCGCCTCGCTCAGCTGCGTGCTGCC  
CGACTTCTTGCAAGGCGCGGCGCGCCAGCTACGTGGGGGCTGCTTCGACAGGCTGCT  
CCACCCGACGCGGTACCCGCCCTTTCCGCACCGTGCCCGTCTTCACACTGCCCTCCCA  
ACTGCCAGACTTCTTGGGGGCCCTGCAGCAGCCTCGCGCCCCGCGTTCCGGGCGGCTCCA  
AGAGAGAGCGGAGCAAGTGTCCCGGGCCCTTCAGCCAGCCCTGGATAGCTACTTCCATCC  
CCCGGGGACTCCCGCGCCGGGACGCGGGGTGGGACCAGGGGCGGGACCTGGGGCGGGGA  
CGGGACTTAAATAAAGGCAGACGCTGTTTTCTAAAAAA

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**FIGURE 364**

MPVPWFLLSLALGRSPVVLSELRLVGPQDATHCSPGLSCRLWDSILCLPGDIVPAPGPV  
LAPTHLQTELVLRCQKETDCDLCLRVAVHLAVHGHWEPEDEEKFGGAADSGVEEPRNAS  
LQAQVVLSTFQAYPTARCVLLEVQVPAALVQFGQSVGSVVYDCFEAALGSEVRIWSYTQPR  
YEKELNHTQQLPALPWLNVVSADGDNVHLVLNVSEEQHFGLSLYWNQVQGPVKPRWHKNLT  
GPQIITLNHTDLVPCLCIQVWPLEPDSVRTNICPFREDPRAHQNLWQAARLRLTLQSWL  
LDAPCSLPAAALCWRAPGGDPCQPLVPPLSWENVTVDKVLEFPPLKGHPNLCVQVNSSE  
KLQEQECLWADSLGPLKDDVLLLETRGPQDNRSLEPSGCTSLPSKASTRAARLGEYL  
LQDLQSGQCLQLWDDDLGALWACPMKYIHKRWALVWLACLLFAAALSLILLKKDHAKG  
WLRLKQDVRSAGAAARGRAALLLYSADDSGFERLVGALASALCQLPLRVAVDLWSRRELS  
AQGPVAFWFAQRRTLQEGGVVLLFSPGAVALCSEWLQDGVSGPGANGPHDAFRASLSC  
VLPDFLQGRAPGSYVGACFDRLHPDAVPALFRTVPVFTLPSQLPDFLQALQPRAPRSG  
RLQERAEQVSRALQPALDSYFHPPGTPAPGRGVGPGAGPGAGDGT

**Signal sequence:**

amino acids 1-20

**Transmembrane domain:**

amino acids 453-475

**N-glycosylation sites:**amino acids 118-121, 186-189, 198-201, 211-214, 238-241,  
248-251, 334-337, 357-360, 391-394**Glycosaminoglycan attachment site:**

amino acids 583-586

**cAMP- and cGMP-dependent protein kinase phosphorylation site:**

amino acids 552-555

**N-myristoylation sites:**amino acids 107-112, 152-157, 319-324, 438-443, 516-521,  
612-617, 692-697, 696-701, 700-705

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**FIGURE 365**

AATAGAAGTCCTCAGGACGGAGCAGAGGTGGCCGGCGGGCCCGGCTGACTGCGCCTCTGC  
TTTCTTTCCATAACCTTTTCTTTTCGGACTCGAATCACGGCTGCTGCGAAGGGTCTAGTTC  
CGGACACTAGGGTGCCCGAACGCGCTGATGCCCCGAGTGCTCGCAGGGCTTCCCGCTAAC  
**CATG**CTGCCGCGCCGCGCGGCCCGCAGCTGCCTTGGCGCTGCCTGTGCTCCTGCTACTGCT  
GGTGGTGCTGACGCGCGCCCCGACCGGCGCAAGGCCATCCCCAGGCCCAGATTACCTGCG  
GCGCGGCTGGATGCGGCTGCTAGCGGAGGGCGAGGGCTGCGCTCCCTGCCGCGCCAGAAGA  
GTGCGCCGCGCGCGGGGCTGCCTGGCGGGCAGGGTGCGCGACGCGTGCGGCTGCTGCTG  
GGAATGCGCCAACCTCGAGGGCCAGCTCTGCGACCTGGACCCCAGTGCTCACTTCTACGG  
GCACTGCGGCGAGCAGCTTGAGTGCCGGCTGGACACAGGCGGCGACCTGAGCCGCGGAGA  
GGTGCCGGAACCTCTGTGTGCCTGTCGTTGCGAGAGTCCGCTCTGCGGGTCCGACGGTCA  
CACCTACTCCAGATCTGCCGCCTGCAGGAGGCGGCCCCGCGCTCGGCCCCGATGCCAACCT  
CACTGTGGCACACCCGGGGCCCTGCGAATCGGGGCCCCAGATCGTGTCACATCCATATGA  
CACTTGGAATGTGACAGGGCAGGATGTGATCTTTGGCTGTGAAGTGTTCCTACCCCAT  
GGCCTCCATCGAGTGGAGGAAGGATGGCTTGACATCCAGCTGCCAGGGGATGACCCCCA  
CATCTCTGTGCAGTTTAGGGGTGGACCCCAGAGGTTTGAGGTGACTGGCTGGCTGCAGAT  
CCAGGCTGTGCGTCCCACTGATGAGGGCACTTACCGCTGCCTTGGCCGCAATGCCCTGGG  
TCAAGTGGAGGCCCCCTGCTAGCTTGACAGTGCTCACACCTGACCAGCTGAACTCTACAGG  
CATCCCCCAGCTGCGATCACTAAACCTGGTTCCCTGAGGAGGAGGCTGAGAGTGAAGAGAA  
TGACGATTACTACT**TAGG**TCCAGAGCTCTGGCCCATGGGGGTGGGTGAGCGGCTATAGTGT  
TCATCCCTGCTCTTGAAAAGACCTGGAAAGGGGAGCAGGGTCCCTTCATCGACTGCTTTC  
ATGCTGTCAGTAGGGATGATCATGGGAGGCCTATTTGACTCCAAGGTAGCAGTGTGGTAG  
GATAGAGACAAAAGCTGGAGGAGGGTAGGGAGAGAAGCTGAGACCAGGACCGGTGGGGTA  
CAAAGGGGCCCCATGCAGGAGATGCCCTGGCCAGTAGGACCTCCAACAGGTTGTTTCCAG  
GCTGGGGTGGGGGCCTGAGCAGACACAGAGGTGCAGGCACCAGGATTCTCCACTTCTTCC  
AGCCCTGCTGGGGCCACAGTTCTAACTGCCCTTCCCTCCCAGGCCCTGGTTCTTGCTATTTTC  
CTGGTCCCCAACGTTTATCTAGCTTGTTTGCCCTTTCCCCAAACTCATCTTCCAGAACTT  
TTCCCTCTCTCCTAAGCCCCAGTTGCACCTACTAACTGCAGTCCCTTTTGCTGTCTGCCG  
TCTTTTGTACAAGAGAGAGAAACAGCGGAGCATGACTTAGTTTCAGTGCAGAGAGATTT

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**FIGURE 366**

MLPPPRPAAALALPVLLLLLVLTTPPTGARPSPGPDYLRRGWMRLLAEGEGCAPCRPEE  
CAAPRGCLAGRVRDACGCCWECANLEGQLCDLDPSAHFYGHCGEQLECRDGTGGDLSRGE  
VPEPLCACRSQSPLCGSDGHTYSQICRLQEAARARPDANLTVAHPGPCESGPQIVSHPYD  
TWNVTGQDVIFGCEVFAYPMASIEWRKDGLDIQLPGDDPHISVQFRGGPQRFVETGWLQI  
QAVRPSDEGTYRCLGRNALGQVEAPASLTVLTPDQLNSTGIPQLRSLNLVPEEEAESEEN  
DDYY

**Important features of the protein:****Signal peptide:**

1-30

**Transmembrane domain:**

None

**N-glycosylation site:**

159-163, 183-187, 277-281

**Tyrosine kinase phosphorylation site:**

244-252

**N-myristoylation site:**

52-58, 66-72, 113-119, 249-255

**Kazal-type serine protease inhibitor domain:**

121-168

**Immunoglobulin domain:**

186-255

**Insulin-like growth factor binding proteins:**

53-90



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**FIGURE 367**

AGACGCTACAGGATGGAGCGGGGCGCAGGAGCCAAGCTGCTGCCGCTGCTGCTGCTTCTG  
CGGGCGACTGGTTTCACATGTGCACAGACAGATGGCCGGAACGGCTACACGGCGGTCATC  
GAAGTGACCAGCGGGGGTCCCTGGGGCGACTGGGCCTGGCCTGAGATGTGTCCCGATGGA  
TTCTTCGCCAGCGGGTTCTCGCTCAAGGTGGAGCCTCCCCAAGGCATTCTGGCGACGAC  
ACTGCACTGAATGGGATCAGGCTGCACTGCGCGCGCGGGAACGTCCTAGGCAATACGCAC  
GTGGTAGAGTCCAGTCTGGAAGCTGGGGCGAATGGAGTGAGCCGCTGTGGTGTCGCGGC  
GGCGCCTACCTAGTGGCTTCTCGCTTCGCGTGGAGGCACCCACGACCCTCGGTGACAAC  
ACAGCAGCGAACAACGTGCGCTTCCGCTGTTTCAGACGGCGAGGAACTGCAGGGGCCTGGG  
CTGAGCTGGGGAGACTTTGGAGACTGGAGTGACCATTGCCCCAAGGGCGCGTGCGGCCTG  
CAGACCAAGATCCAGGGACCTAGAGGCCTCGGCGATGACACTGCGCTGAACGACGCGCGC  
TTATTCTGCTGCCGCAGTTGAACGGCGCGCGCCGCGCTCTCTCCCGGGCCAGGAGGC  
TAGTCCACCTCTTGCTATTAAAGCTTCTCTGAGTTG

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**FIGURE 368**

MERGAGAKLLPLLLLLLRATGFTCAQTDGRNGYTAVIEVTSGGPWGDWAWPEMCPDGFFAS  
GFSLKVEPPQGI PGDDTALNGIRLHCARGNVLGNTHVVESQSGSWGGEWSEPLWCRGGAYL  
VAFSLRVEAPTTLGDNNTAANNVRFRCS DGEELQGPGLSWGDFGDWSDHCPKGACGLQTKI  
QGPRGLGDDTALNDARLFCCRS

**Important features of the protein:****Signal peptide:**

1-24

**Transmembrane domain:**

None

**N-myristoylation site:**

41-47

89-95

156-162

**Growth factor and cytokines receptors family signature 2:**

103-110

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**FIGURE 369**

GCCAACACTGGCCAAACCTCGGAGACCGTCCTGCGCTCTCTGGAGACGCGCTGTCCGCGC  
CCAGGGTGGTGCCATGTGGGGCGCTCGCCGCTCGTCCGTCTCCTCATCCTGGAACGCCGC  
TTCGCTCCTGCAGCTGCTGCTGGCTGCGCTGCTGGCGGCGGGGGCGAGGGCCAGCGGCGA  
GTACTGCCACGGCTGGCTGGACGCGCAGGGCGTCTGGCGCATCGGCTTCCAGTGTCCCGA  
GCGCTTCGACGGCGGCGACGCCACCATCTGCTGCGGCAGCTGCGCGTTGCGCTACTGCTG  
CTCCAGCGCCGAGGCGCGCCTGGACCAGGGCGGCTGCGACAATGACCGCCAGCAGGGCGC  
TGGCGAGCCTGGCCGGGCGGACAAAGACGGCCCCGACGGCTCGGCAGTGCCCCATCTACGT  
GCCGTTCTCATTTGTTGGCTCCGTGTTTGTGCGCTTTATCATCTTGGGGTCCCTGGTGGC  
AGCCTGTTGCTGCAGATGTCTCCGGCCTAAGCAGGATCCCCAGCAGAGCCGAGCCCCAGG  
GGGTAACCGCTTGATGGAGACCATCCCCATGATCCCCAGTGCCAGCACCTCCCGGGGGTC  
GTCCTCAGCCAGTCCAGCACAGCTGCCAGTTCCAGCTCCAGCGCCAACTCAGGGGGCCCG  
GGCGCCCCCAACAAGGTCACAGACCAACTGTTGCTTGCCGGAAGGGACCATGAACAACGT  
GTATGTCAACATGCCCCACGAATTTCTCTGTGCTGAACTGTCAGCAGGCCACCCAGATTGT  
GCCACATCAAGGGCAGTATCTGCATCCCCCATACTGGGGTACACGGTGCAGCACGACTC  
TGTGCCCATGACAGCTGTGCCACCTTTCATGGACGGCCTGCAGCCTGGCTACAGGCAGAT  
TCAGTCCCCCTTCCCTCACACCAACAGTGAACAGAAGATGTACCCAGCGGTGACTGTATA  
ACCGAGAGTCACTGGTGGGTTTCCTTTACTGAAGGGAGACGAAGGCAGGGGTGGATTTTCG  
AGGTGGAAGT

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**FIGURE 370**

MWGARRSSVSSSWNAASLLQLLLAALLAAGARASGEYCHGWLDAQGVWRIGFQCPERFDG  
GDATICCGSCALRYCCSSAEARLDQGGCDNDRQQGAGEPGRADKDGPDGSAPVIYVPFLI  
VGSVFVAFIILGSLVAACCCRLRPKQDPQQSRAPGGNRLMETIPMIPSASTSRGSSSRQ  
SSTAASSSSSANS GARAPPTRSQTNCCLEGTMMNVYVNMPTNFSVLNCQQATQIVPHQG  
QYLHPPYVGYTVQHDSVPMTAVPPFMDGLQPGYRQIQSPFPHTNSEQKMPAVTV

**Important features of the protein:****Signal peptide:**

1-33

**Transmembrane domain:**

54-78

**N-glycosylation site:**

223-226

**cAMP- and cGMP-dependent protein kinase phosphorylation site:**

5-8

**N-myristoylation site:**

3-8, 30-35, 60-65, 86-91, 132-137, 211-216, 268-273

**Prokaryotic membrane lipoprotein lipid attachment site:**

128-138

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## FIGURE 371

CACCAGACAGCACTCCAGCACTCTGTTTGGGGGGCATTGAAACAGCAAAATCACTCATA  
AAAGGCAAAAAATTGCAAAAAAATAGTAATAACCAGCATGGCACTAAATAGACCATGA  
AAAGACATGTGTGTGCAGTATGAAAATTGAGACAGGAAGGCAGAGTGTCTGCTGTTCCA  
CCTCAGCTGGGAATGTGCATCAGGCAACTCAAGTTTTTACCACGGCATGTGTCTGTGAA  
TGTCCGCAAAACATTCTCTCTCCCCAGCCTTCATGTGTAACTGGGGATGATGTGGACC  
TGGGCACTGTGGATGCTCCCTTCACTCTGCAAATTCAGCCTGGCAGCTCTGCCAGCTAAG  
CCTGAGAACATTTCTGTGTCTACTACTATAGGAAAAATTTAACTGCACTTGGAGTCCA  
GGAAAGGAAACCAGTTATACCCAGTACACAGTTAAGAGAACTTACGCTTTTGGAGAAAA  
CATGATAATTGTACAACCAATAGTTCTACAAGTGAAATCGTGCTTCGTGCTCTTTTTTC  
CTTCCAAGAATAACGATCCCAGATAATTATACCATTGAGGTGGAAGCTGAAAATGGAGAT  
GGTGTAAATTAATCTCATATGACATACTGGAGATTAGAGAACATAGCGAAAATGAACCA  
CCTAAGATTTTCCGTGTGAAACCAAGTTTTGGGCATCAAACGAATGATTCAAATTGAATGG  
ATAAAGCCTGAGTTGGCGCCTGTTTCATCTGATTTAAAATACACACTTCGATTCAAGACA  
GTCAACAGTACCAGCTGGATGGAAGTCAACTTCGCTAAGAACCCTAAGGATAAAAAACCAA  
ACGTACAACCTCACGGGGCTGCAGCCTTTTACAGAAATATGTCATAGCTCTGCGATGTGCG  
GTCAAGGAGTCAAAGTCTGGAGTGACTGGAGCCAAGAAAAAATGGGAATGACTGAGGAA  
GAAGCTCCATGTGGCCTGGAAGTGTGGAGAGTCTGAAACCAGCTGAGGCGGATGGAAGA  
AGGCCAGTGCCTGTTGTTATGGAAGAAGGCAAGAGGAGCCCCAGTCCTAGAGAAAACACTT  
GGCTACAACATATGGTACTATCCAGAAAGCAACACTAACCTCACAGAAACAATGAACACT  
ACTAACCCAGCAGCTTGAAGTGCATCTGGGAGGCGAGAGCTTTTGGGTGTCTATGATTTCT  
TATAATTCTCTTGGGAAGTCTCCAGTGGCCACCCTGAGGATTCCAGCTATTCAAGAAAA  
TCATTTCAAGTGCATTGAGGTGATGCAGGCCTGCGTTGCTGAGGACCAGCTAGTGGTGAAG  
TGGCAAAGCTCTGCTCTAGACGTGAACACTTGGATGATTGAATGGTTTTCCGGATGTGGAC  
TCAGAGCCCCACCACCTTTCTGGGAATCTGTGTCTCAGGCCACGAACTGGACGATCCAG  
CAAGATAAATTAACCTTTCTGGTGCTATAACATCTCTGTGTATCCAATGTTGCATGAC  
AAAGTTGGCGAGCCATATTCATCCAGGCTTATGCCAAAGAAGGCGTTCCATCAGAAGGT  
CCTGAGACCAAGGTGGAGAACATTGGCGTGAAGACGGTCACGATCACATGGAAAGAGATT  
CCCAAGAGTGAGAGAAAGGGTATCATCTGCAACTACACCATCTTTTACCAAGCTGAAGGT  
GGAAAAGGATTCTGTAAGCACGCCCATAGCGAAGTGGAAGAAAAACCCCAAGCCCCAGATA  
GATGCTATGGATAGACCTGTTGTAGGCATGGCTCCCCCATCTCATTGTGACTTGCAACCT  
GGCATGAATCACTTAGCTTCTTTAAATCTCTCTGAAAATGGGGCCAAGAGCACCCACCTT  
TTGGGGTTTTTGGGGTTAAATGAGAGTGAAGTGACAGTACCTGAGAGGAGAGTCTGAGG  
AAATGGAAGGAGTTGTTATAATTTGTCTGTTAGGCCCTGAATTGACCTCCCGGGAGCT  
CCCCGACCATCATTCCCAGGAATGGCGTGCCTGGCTTAAAGAGTGAGGAGGAACAGACCC  
TGTCACCATGACTTCTACTGCCCCTGCCAAATCATGCTTTTGTTTTTTCAGTCCACCTTAT  
CTCCTGACATCTTAAATACTGGGCAAGGCTTGGATTCTTGCTTAGGCTAAATAATTTTTT  
CTTATGGTAAAAATACAGTAAAAATATTTTTCCAGTTTAAACATTTGAAAGTGTAATTT  
AGTGGCATTAGAAGCATTCACAATATTGTGCAACCATCACCCTATTTCCAGAACTCTTC  
TATTTCTGCCCCAATAGAAGCCCTATACCCATTCTAGTCACTCCCCATTCTCTCCTC  
CCACAGCCCCCTGGCAACTACCAACTGCTTTGTGTCTCTATGGATTGCCTATTTTGGATA  
TTTCATATACATAGAATCATAAANTAAAAA

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**FIGURE 372**

MCIRQLKFFTTACVCECPQNILSPQPSCVNLGMMWTWALWMLPSLCKFSLAALPAKPENI  
SCVYYYRKNLTCTWSPGKETSYTQYTVKRTYAFGEKHDNCTNSSTSENRASCSFFLPRI  
TIPDNYTIEVEAENG DGV KSHMTYWRL ENIAKTEPPKIFRVKPV LGIKRMIQIEWIKPE  
LAPVSSDLKYTLRFRTVNSTSWMEVNF AKNRKDKNQTYNLTGLQPFT EYVIALRC AVKES  
KFWS DWSQEKMG MTEEEAPCGLELWRVLKPAEADGR RPVRL L WKKARGAPVLEKTLGYN I  
WYYPESNTNLTETMNTTNQQLHLGGESFWVSMISYNSLGKSPVATLRIPAIQEKSFQC  
IEVMQACVAEDQLVVKWQSSALDVNTWMIEWFPD VDSEPTTLSWESVSQATNWTIQQDKL  
KPFWCYNISVYPMLHDKVGEPYSIQAYAKEGVPSEGPETKVENIGVKT V TITWKEIPKSE  
RKG IICNYTIFYQAEGGKGFC KHAHSEVEKNPKPQIDAMDRPVVGMAPP SHCDLQPGMNH  
LASLN LSENGAKSTHLLGFWGLNESEVTV PERRVLRKWKELL

**Important features of the protein:****Signal peptide:**

1-46

**Transmembrane domain:**

None

**N-glycosylation site:**59-63, 69-73, 99-103, 103-107, 125-129, 198-202, 215-219, 219-  
223, 309-313, 315-319, 412-416, 427-431, 487-491, 545-549, 563-  
567**N-myristoylation site:**

32-38, 137-143, 483-489, 550-556, 561-567

**Amidation site:**

274-278

**Growth factor and cytokines receptors family signature 1:**

62-75

**Fibronectin type III domain:**

54-144

154-247

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**FIGURE 373**

CCAGGTCCAACCTGCACCTCGGTTCTATCGATTGAATTCCCCGGGGATCCTCTAGAGATCC  
CTCGACCTCGACCCACGCGTCCGCCAAGCTGGCCCTGCACGGCTGCAAGGGAGGCTCCTG  
TGGACAGGCCAGGCAGGTGGGCCTCAGGAGGTGCCTCCAGGCGGCCAGTGGGCCTGAGGC  
CCCAGCAAGGGCTAGGGTCCATCTCCAGTCCCAGGACACAGCAGCGGCCACCATGGCCAC  
GCCTGGGCTCCAGCAGCATCAGCAGCCCCCAGGACCGGGGGAGGCACAGGTGGCCCCCAC  
CACCCGGAGGAGCAGCTCCTGCCCCCTGTCCGGGGGATGACTGATTCTCCTCCGCCAGGCC  
ACCCAGAGGAGAAGGCCACCCCGCCTGGAGGCACAGGCCATGAGGGGCTCTCAGGAGGTG  
CTGCTGATGTGGCTTCTGGTGTGGCAGTGGGCGGCACAGAGCACGCCTACCGGCCCGGC  
CGTTAGGGTGTGTGCTGTCCCGGGCTCACGGGGACCTGTCTCCGAGTCGTTTCGTGCAGC  
GTGTGTACCAGCCCTTCCTCACCACCTGCGACGGGCACCGGGCCTGCAGCACCTACCGAA  
CCATTTATAGGACCGCTACCGCCGCAGCCCTGGGCTGGCCCCCTGCCAGGCCTCGCTACG  
CGTGCTGCCCCGGCTGGAAGAGGACCAGCGGGCTTCCTGGGGCCTGTGGAGCAGCAATAT  
GCCAGCCGCCATGCCGGAACGGAGGGAGCTGTGTCCAGCCTGGCCGCTGCCGCTGCCCTG  
CAGGATGGCGGGGTGACACTTGCCAGTCAGATGTGGATGAATGCAGTGCTAGGAGGGGCG  
GCTGTCCCCAGCGCTGCATCAACACCGCCCGCAGTTACTGGTGCCAGTGTTGGGAGGGGC  
ACAGCCTGTCTGCAGACGGTACACTCTGTGTGCCCCAAGGGAGGGCCCCCAGGGTGGCCC  
CCAACCCGACAGGAGTGGACAGTGCAATGAAGGAAGAAGTGCAGAGGCTGCAGTCCAGGG  
TGGACCTGCTGGAGGAGAAGCTGCAGCTGGTGCTGGCCCCACTGCACAGCCTGGCCTCGC  
AGGCACTGGAGCATGGGCTCCCGGACCCCGCAGCCTCCTGGTGCACTCCTTCCAGCAGC  
TCGGCCGCATCGACTCCCTGAGCGAGCAGATTTTCCTTCCTGGAGGAGCAGCTGGGGTCCT  
GCTCCTGCAAGAAAGACTCGTGACTGCCCCAGCGCCCCAGGCTGGACTGAGCCCCCTCACGC  
CGCCCTGCAGCCCCCATGCCCCCTGCCCAACATGCTGGGGGTCCAGAAGCCACCTCGGGGT  
GACTGAGCGGAAGGCCAGGCAGGGCCTTCCTCCTTTTCCTCCTCCCCTTCCCTCGGGAGG  
GTCCCCAGACCTGGCATGGGATGGGCTGGGATTTTTTTTGTGAATCCACCCCTGGCTAC  
CCCCACCTGGTTACCCCAACGGCATCCCAAGGCCAGGTGGGCCCTCAGCTGAGGGAAGG  
TACGAGTTCCCCTGCTGGAGCCTGGGACCCATGGCACAGGCCAGGCAGCCCGGAGGCTGG  
GTGGGGCCTCAGTGGGGGCTGCTGCCTGACCCCCAGCACATAAAAAATGAAACGTGAAAA  
AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAGGGCGGCCGCGACTCTAGAGTC  
GACCTGCAGAAGCTTGGCCGCCATGGCCCACTTGTTTATTGCAGCTTATAATGGTTACAAAT

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**FIGURE 374**

MTDSPPPGHPPEEKATPPGGTGHEGLSGGAADVASGVGSGRHRARLPARPLGCVLSRAHGD  
PVSESFVQRVYQPFLTTCDGHRACSTYRTIYRTAYRRSPGLAPARPRYACCPGWKRTSGL  
PGACGAAICQPPCRNGGSCVQPGRCRCPAGWRGDTQCQSDVDECSARRGGCPQRCINTAGS  
YWCQCWEGHSLADGTLCPKGGPPRVAPNPTGVDSAMKEEVQRLQSRVDLLEEKQLVL  
APLHSLASQALEHGLPDPGSLLVHSFQQLGRIDSLSEQISFLEEQLGSCSCKKDS



Wholemound In Situ with PRO1449 Orthologue

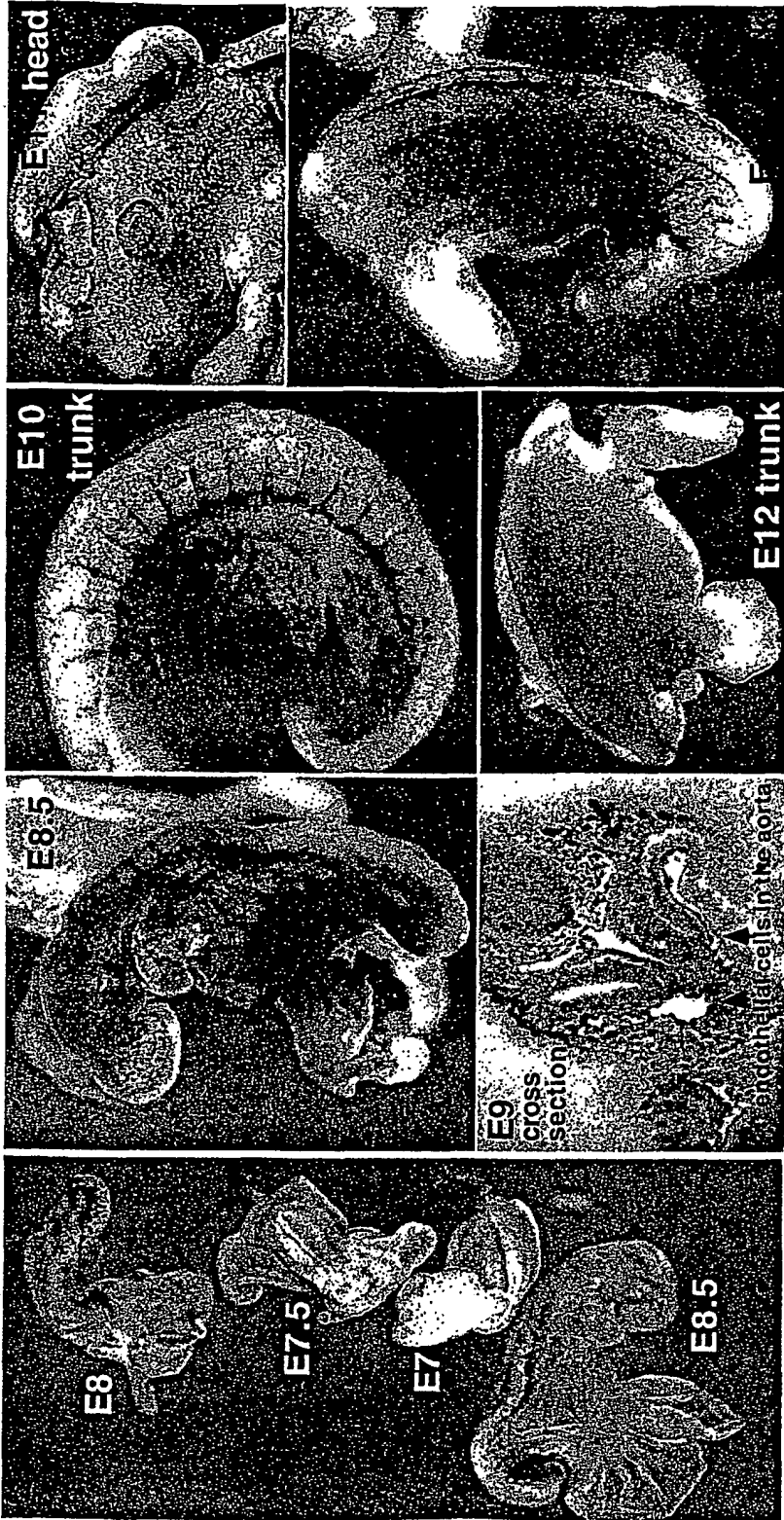
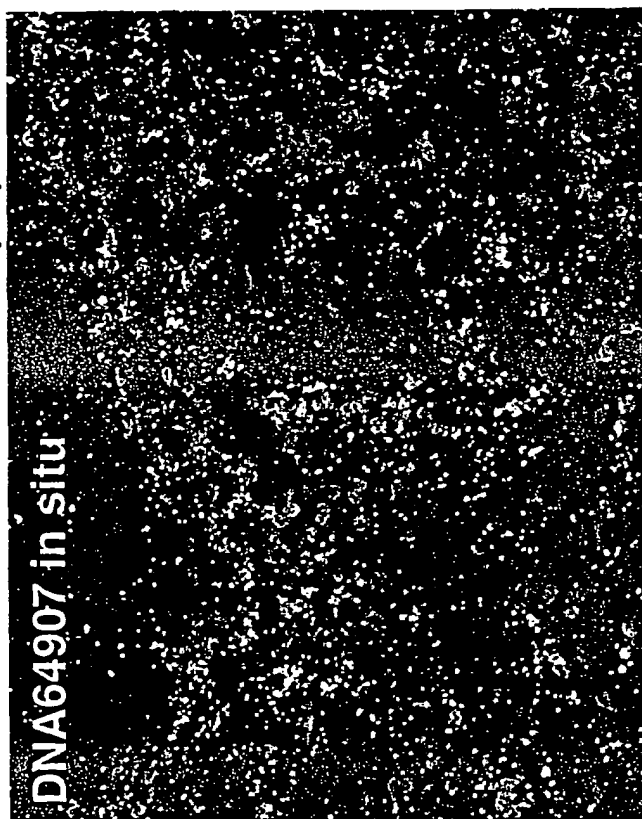


FIGURE 375

PRO1449 is expressed in vasculature of many inflamed and diseased tissues

Human tumor tissue (DF)



DNA64907 in situ

Human tumor tissue (BF)

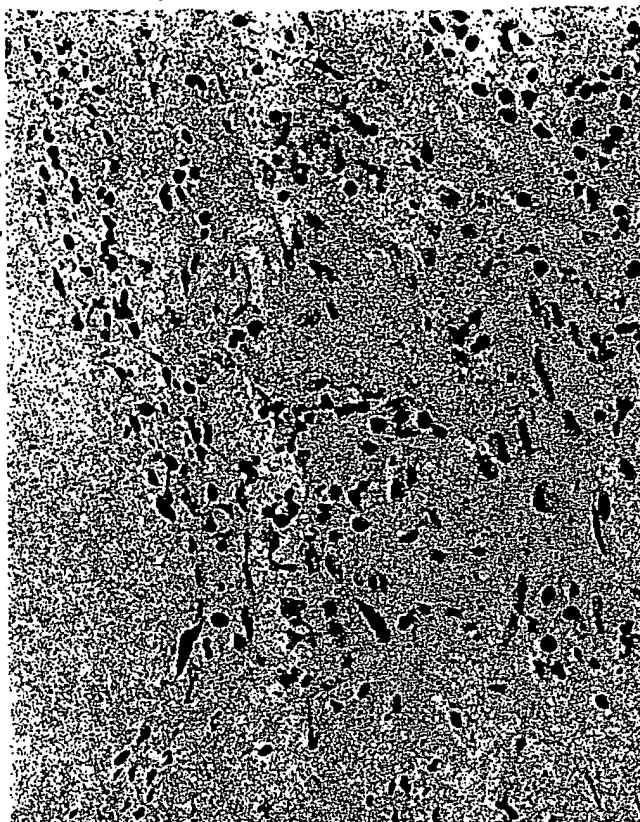


FIGURE 376

Mouse orthologue of PRO1449 induces ectopic vessels in the eyes of chicken embryos

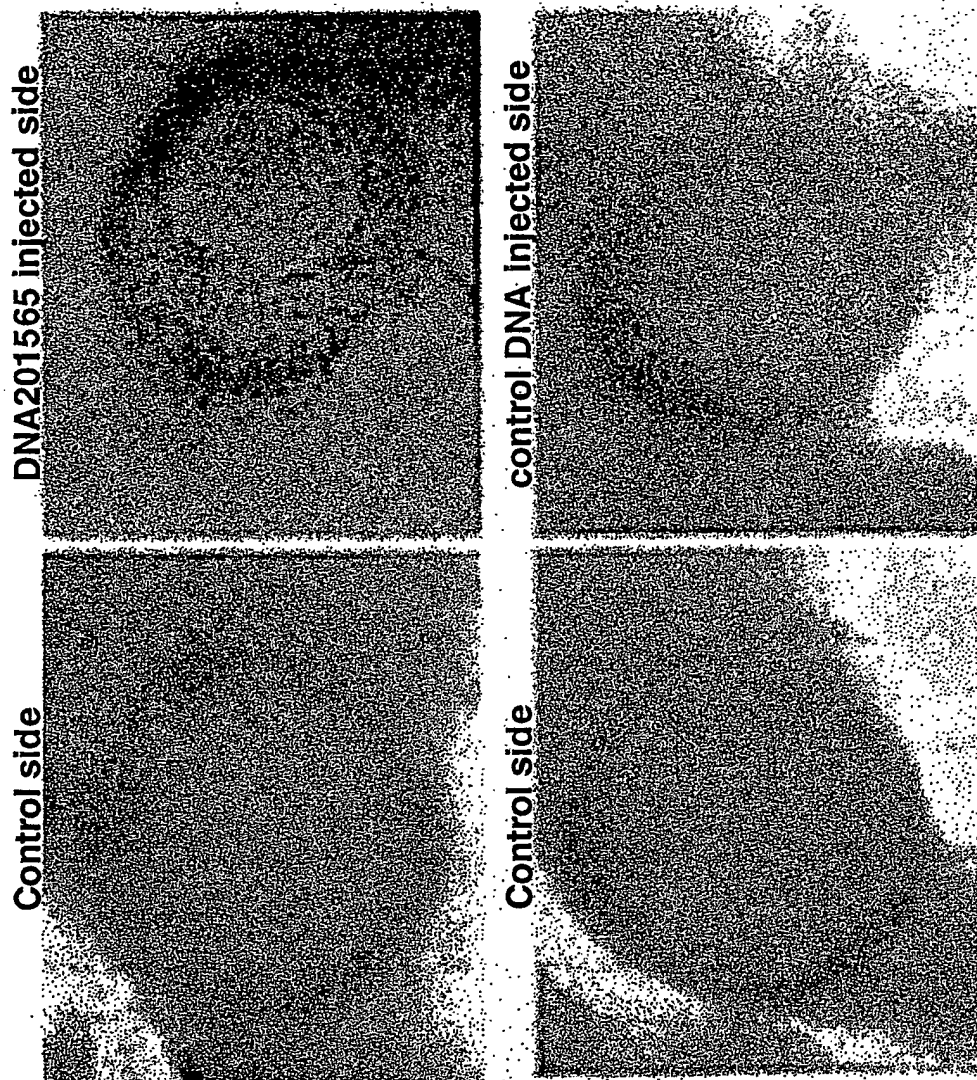


FIGURE 377

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|----------------|--------------------------------|----|
| 60/219,556     | 20 July 2000 (20.07.2000)      | US |
| 60/220,624     | 25 July 2000 (25.07.2000)      | US |
| 60/220,664     | 25 July 2000 (25.07.2000)      | US |
| PCT/US00/20710 | 28 July 2000 (28.07.2000)      | US |
| 60/222,695     | 2 August 2000 (02.08.2000)     | US |
| 09/643,657     | 17 August 2000 (17.08.2000)    | US |
| PCT/US00/23522 | 23 August 2000 (23.08.2000)    | US |
| PCT/US00/23328 | 24 August 2000 (24.08.2000)    | US |
| 60/230,978     | 7 September 2000 (07.09.2000)  | US |
| 60/000,000     | 15 September 2000 (15.09.2000) | US |
| 09/664,610     | 18 September 2000 (18.09.2000) | US |
| 09/665,350     | 18 September 2000 (18.09.2000) | US |
| 60/242,922     | 24 October 2000 (24.10.2000)   | US |
| 09/709,238     | 8 November 2000 (08.11.2000)   | US |
| PCT/US00/30952 | 8 November 2000 (08.11.2000)   | US |
| PCT/US00/30873 | 10 November 2000 (10.11.2000)  | US |
| PCT/US00/32678 | 1 December 2000 (01.12.2000)   | US |
| 09/747,259     | 20 December 2000 (20.12.2000)  | US |
| PCT/US00/34956 | 20 December 2000 (20.12.2000)  | US |
| 09/767,609     | 22 January 2001 (22.01.2001)   | US |
| 09/796,498     | 28 February 2001 (28.02.2001)  | US |
| PCT/US01/06520 | 28 February 2001 (28.02.2001)  | US |
| PCT/US01/06666 | 1 March 2001 (01.03.2001)      | US |
| 09/802,706     | 9 March 2001 (09.03.2001)      | US |
| 09/808,689     | 14 March 2001 (14.03.2001)     | US |
| 09/816,744     | 22 March 2001 (22.03.2001)     | US |
| 09/828,366     | 5 April 2001 (05.04.2001)      | US |
- (71) Applicant (for all designated States except US): **GENENTECH, INC.** [US/US]; 1 DNA Way, South San Francisco, CA 94080-4990 (US).
- (71) Applicants and
- (72) Inventors: **BAKER, Kevin, P.** [GB/US]; 14006 Indian Run Drive, Darnestown, MD 20878 (US). **FERRARA, Napoleone** [US/US]; #704, 2090 Pacific Avenue, San Francisco, CA 94109 (US). **GERBER, Hanspeter** [CH/US]; #5, 1121 Tennessee Street, San Francisco, CA 94107 (US). **GERRITSEN, Mary, E.** [CA/US]; 541 Parrott Drive, San Mateo, CA 94402 (US). **GODDARD, Audrey** [CA/US]; 110 Congo Street, San Francisco, CA 94131 (US). **GODOWSKI, Paul, J.** [US/US]; 2627 Easton Drive, Burlingame, CA 94010 (US). **GURNEY, Austin, L.** [US/US]; 1 Debbie Lane, Belmont, CA 94002 (US). **HILLAN, Kenneth, J.** [GB/US]; 64 Seward Street, San Francisco, CA 94114 (US). **MARSTERS, Scot, A.** [US/US]; 990 Cherry Street, San Carlos, CA 94070 (US). **PAN, James** [CA/US]; 2705 Coronet Boulevard, Belmont, CA 94002 (US). **PAONI, Nicholas, F.** [US/US]; 1756 Terrace Drive, Belmont, CA 94002 (US). **STEPHAN, Jean-Philippe, F.** [FR/US]; 320 C Lansdale Avenue, Millbrae, CA 94030 (US). **WATANABE, Colin, K.** [US/US]; 128 Corliss Drive, Moraga, CA 94556 (US). **WILLIAMS, P., Mickey** [US/US]; 509 Alto Avenue, Half Moon Bay, CA 94019 (US). **WOOD, William, I.** [US/US]; 35 Southdown Court, Hillsborough, CA 94010 (US).
- (72) Inventor; and
- (75) Inventor/Applicant (for US only): **YE, Weilan** [CN/US]; 119 Barkentine Street, Foster City, CA 94404 (US).

[Continued on next page]

(54) Title: COMPOSITIONS AND METHODS FOR THE DIAGNOSIS AND TREATMENT OF DISORDERS INVOLVING ANGIOGENESIS

(57) Abstract: Compositions and methods are disclosed for stimulating or inhibiting angiogenesis and/or cardiovascularization in mammals, including humans. Pharmaceutical compositions are based on polypeptides or antagonists thereto that have been identified for one or more of these uses. Disorders that can be diagnosed, prevented, or treated by the compositions herein include trauma such as wounds, various cancers, and disorders of the vessels including atherosclerosis and cardiac hypertrophy. In addition, the present invention is directed to novel polypeptides and to nucleic acid molecules encoding those polypeptides. Also provided herein are vectors and host cells comprising those nucleic acid sequences, chimeric polypeptide molecules comprising the polypeptides of the present invention fused to heterologous polypeptide sequences, antibodies which bind to the polypeptides of the present invention and to methods for producing the polypeptides of the present invention.

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(74) Agents: AGARWAL, Atulya, R. et al.; c/o Genentech, Inc., MS49, 1 DNA Way, South San Francisco, CA 94080-4990 (US).

patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

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## A. CLASSIFICATION OF SUBJECT MATTER

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## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, EMBL

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages   | Relevant to claim No.                 |
|------------|--|---------------------------------------|
| X          | WO 99 46281 A (BAKER KEVIN P ;CHEN JIAN (US); GENENTECH INC (US); GURNEY AUSTIN ()<br>16 September 1999 (1999-09-16)<br>figures 128,129<br>---   | 1-19                                  |
| X          | WO 99 43802 A (KATO SEISHI ;KIMURA TOMOKO (JP); PROTEGENE INC (JP); SEKINE SHINGO)<br>2 September 1999 (1999-09-02)<br><br>see SEQ ID NOS:4 and 21<br>page 28, line 24 -page 29, line 2<br>page 34, line 18 - line 25<br>---<br>-/-- | 1-21,23,<br>25,27,<br>31,34,<br>35,42 |

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents :

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Date of the actual completion of the international search

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Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

MADDOX, A

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/21735

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages   | Relevant to claim No.                 |
|------------|--|---------------------------------------|
| X          | WO 99 50405 A (GENETICS INST)<br>7 October 1999 (1999-10-07)<br><br>page 39, line 14 -page 40, line 13<br>page 67, line 29 -page 68, line 2<br>See SEQ ID NOS:11 and 12<br>page 73, line 14 - line 22<br>---   | 1-21,23,<br>25,27,<br>31,34,<br>35,42 |
| X          | DATABASE SWISSPROT [Online]<br>30 May 2000 (2000-05-30)<br>"Cornichon homolog (TGAM77)."<br>Database accession no. 095406<br>XP002210332<br>abstract<br>-& DATABASE EMBL [Online]<br>29 December 1998 (1998-12-29)<br>"Homo sapiens cornichon mRNA, complete<br>cds."<br>Database accession no. AF104398<br>XP002210333<br>the whole document<br>--- | 1-4,11,<br>12,18,19                   |
| P,X        | WO 00 53751 A (BAKER KEVIN P ;GENENTECH<br>INC (US); NAPIER MARY A (US); ASHKENAZI A)<br>14 September 2000 (2000-09-14)<br>figures 1,2<br>---  | 1-19                                  |
| P,X        | WO 00 53756 A (BOTSTEIN DAVID;BAKER KEVIN<br>P ; GENENTECH INC (US); ASHKENAZI AVI J)<br>14 September 2000 (2000-09-14)<br>figures 128,129<br>---  | 1-19                                  |
| E          | WO 02 00690 A (FERRARA NAPOLEONE ;STEPHAN<br>JEAN PHILIPPE F (US); WILLIAMS P MICKEY)<br>3 January 2002 (2002-01-03)<br>page 13, line 29 -page 14, line 17; claims<br>37,41; figures 1,2; examples 21,22<br>---  | 1-35,37,<br>42                        |
| A          | WO 00 32221 A (FERRARA NAPOLEONE ;WILLIAMS<br>P MICKEY (US); BAKER KEVIN P (US); GEN)<br>8 June 2000 (2000-06-08)<br>the whole document<br>---   |                                       |
| A          | WO 00 15792 A (WILLIAMS P MICKEY<br>;GENENTECH INC (US); FONG SHERMAN (US);<br>GODDARD) 23 March 2000 (2000-03-23)<br>the whole document<br>-----  |                                       |

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 01/21735

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 20-35 37 and 42 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:  
1-35, 37, 42 all partially

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.



FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

## Continuation of Box I.2

Present claims 20-28,31,34,35,37 and 42 relate to a product/compound/method defined by reference to a desirable characteristic or property, namely antagonist and agonist. The claims cover all products/compounds/methods having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such products/compounds/methods. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product/compound/method by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the products/compounds/methods where the antagonist and agonist are antibodies as defined by claims 29,30,32,and 33.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

Invention 1: Claims 1-35 37 42 all partially

Isolated nucleic acid molecule and corresponding polypeptide defined by SEQ ID NOS:1 and 2(P0181),host,vectors,antibody and methods based on said sequences.

Inventions 2-187: Claims 1-43 in so far as applicable

Nucleic acid molecule and corresponding polypeptide as defined by uneven numbered SEQ ID NOS:3-373 and the encoded product defined by the even SEQ ID NOS:4-374, wherein each individual molecule and corresponding polypeptide represent a single invention such that invention 2 is represented by SEQ ID NOS:3 and 4 each subsequent pair of sequences representing another invention through to invention 187 being represented by SEQ ID NOS:373 and 374;host,vectors,antibody and methods based on said sequences.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 01/21735

| Patent document<br>cited in search report |   | Publication<br>date | Patent family<br>member(s) | Publication<br>date |
|---|---|---------------------|----------------------------|---------------------|
| WO 9946281                                | A | 16-09-1999          | US 6391311 B1              | 21-05-2002          |
|   |   |                     | AU 3072199 A               | 27-09-1999          |
|   |   |                     | CA 2321677 A1              | 16-09-1999          |
|   |   |                     | US 2002127584 A1           | 12-09-2002          |
|   |   |                     | US 2002094416 A1           | 18-07-2002          |
|   |   |                     | WO 9946281 A2              | 16-09-1999          |
|   |   |                     | US 2002156006 A1           | 24-10-2002          |
|   |   |                     | US 2002169284 A1           | 14-11-2002          |
|   |   |                     | ZA 9901937 A               | 17-04-2000          |
|   |   |                     | EP 1241187 A2              | 18-09-2002          |
|   |   |                     | AU 3075099 A               | 11-10-1999          |
|   |   |                     | CA 2322792 A1              | 23-09-1999          |
|   |   |                     | EP 1064382 A2              | 03-01-2001          |
|   |   |                     | WO 9947677 A2              | 23-09-1999          |
|   |   |                     | US 6455283 B1              | 24-09-2002          |
|   |   |                     | EP 1241183 A2              | 18-09-2002          |
|   |   |                     | US 2002072496 A1           | 13-06-2002          |
|   |   |                     | US 2002142961 A1           | 03-10-2002          |
|   |   |                     | US 2002072067 A1           | 13-06-2002          |
|   |   |                     | US 2002072092 A1           | 13-06-2002          |
|   |   |                     | US 2002072497 A1           | 13-06-2002          |
|   |   |                     | US 2002103125 A1           | 01-08-2002          |
|   |   |                     | US 2002123463 A1           | 05-09-2002          |
|   |   |                     | US 2002132252 A1           | 19-09-2002          |
|   |   |                     | US 2002127576 A1           | 12-09-2002          |
|   |   |                     | US 2002132253 A1           | 19-09-2002          |
|   |   |                     | US 2002160384 A1           | 31-10-2002          |
|   |   |                     | AU 735081 B2               | 28-06-2001          |
|   |   |                     | AU 1532499 A               | 15-06-1999          |
|   |   |                     | CA 2309358 A1              | 03-06-1999          |
|   |   |                     | EP 1241180 A2              | 18-09-2002          |
|   |   |                     | EP 1032667 A2              | 06-09-2000          |
|   |   |                     | WO 9927098 A2              | 03-06-1999          |
|   |   |                     | US 6410708 B1              | 25-06-2002          |
|   |   |                     | EP 1241185 A2              | 18-09-2002          |
|   |   |                     | EP 1249491 A2              | 16-10-2002          |
|   |   |                     | EP 1251139 A2              | 23-10-2002          |
|   |   |                     | US 2002161199 A1           | 31-10-2002          |
|   |   |                     | EP 1241179 A2              | 18-09-2002          |
|   |   |                     | EP 1241186 A2              | 18-09-2002          |
|   |   |                     | AU 741133 B2               | 22-11-2001          |
|   |   |                     | AU 3757099 A               | 08-11-1999          |
|   |   |                     | CA 2324297 A1              | 28-10-1999          |
|   |   |                     | EP 1071773 A1              | 31-01-2001          |
|   |   |                     | JP 2002512032 T            | 23-04-2002          |
|   |   |                     | WO 9954467 A1              | 28-10-1999          |
|   |   |                     | US 2002147322 A1           | 10-10-2002          |
|   |   |                     | EP 1241251 A2              | 18-09-2002          |
|   |   |                     | US 2002119118 A1           | 29-08-2002          |
| WO 9943802                                | A | 02-09-1999          | AU 2549399 A               | 15-09-1999          |
|   |   |                     | CA 2322711 A1              | 02-09-1999          |
|   |   |                     | EP 1056847 A2              | 06-12-2000          |
|   |   |                     | WO 9943802 A2              | 02-09-1999          |
|   |   |                     | JP 2002506615 T            | 05-03-2002          |
| WO 9950405                                | A | 07-10-1999          | AU 3457299 A               | 18-10-1999          |
|   |   |                     | CA 2324492 A1              | 07-10-1999          |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 01/21735

| Patent document<br>cited in search report | Publication<br>date | Patent family<br>member(s) | Publication<br>date |
|---|---------------------|----------------------------|---------------------|
| WO 9950405                                | A                   | EP 1068307 A1              | 17-01-2001          |
|   |                     | JP 2002509722 T            | 02-04-2002          |
|   |                     | WO 9950405 A1              | 07-10-1999          |
| -----                                     |                     |                            |                     |
| WO 0053751                                | A                   | 14-09-2000                 |                     |
|   |                     | AU 1748200 A               | 19-06-2000          |
|   |                     | AU 1749900 A               | 12-07-2000          |
|   |                     | AU 2192800 A               | 12-07-2000          |
|   |                     | AU 2224800 A               | 28-09-2000          |
|   |                     | AU 2399300 A               | 28-09-2000          |
|   |                     | AU 2495200 A               | 28-09-2000          |
|   |                     | AU 2596700 A               | 28-09-2000          |
|   |                     | AU 2600800 A               | 28-09-2000          |
|   |                     | AU 2879400 A               | 31-07-2001          |
|   |                     | AU 2883600 A               | 28-09-2000          |
|   |                     | AU 3072199 A               | 27-09-1999          |
|   |                     | AU 3107700 A               | 28-09-2000          |
|   |                     | AU 3381600 A               | 28-09-2000          |
|   |                     | AU 3514400 A               | 28-09-2000          |
|   |                     | CA 2321677 A1              | 16-09-1999          |
|   |                     | EP 1173563 A1              | 23-01-2002          |
|   |                     | EP 1159419 A1              | 05-12-2001          |
|   |                     | EP 1220905 A2              | 10-07-2002          |
|   |                     | EP 1135485 A2              | 26-09-2001          |
|   |                     | EP 1141284 A2              | 10-10-2001          |
|   |                     | EP 1159422 A1              | 05-12-2001          |
|   |                     | EP 1141289 A2              | 10-10-2001          |
|   |                     | US 2002119130 A1           | 29-08-2002          |
|   |                     | WO 0053753 A2              | 14-09-2000          |
|   |                     | WO 0053754 A1              | 14-09-2000          |
|   |                     | WO 0053755 A2              | 14-09-2000          |
|   |                     | WO 0153486 A1              | 26-07-2001          |
|   |                     | WO 0053756 A2              | 14-09-2000          |
|   |                     | WO 0053757 A2              | 14-09-2000          |
|   |                     | WO 0053758 A2              | 14-09-2000          |
|   |                     | US 2002127584 A1           | 12-09-2002          |
|   |                     | US 2002094416 A1           | 18-07-2002          |
|   |                     | WO 0032221 A2              | 08-06-2000          |
|   |                     | WO 0053750 A1              | 14-09-2000          |
|   |                     | WO 0037638 A2              | 29-06-2000          |
|   |                     | WO 0037640 A2              | 29-06-2000          |
|   |                     | WO 0053751 A1              | 14-09-2000          |
|   |                     | WO 0053752 A2              | 14-09-2000          |
|   |                     | US 2002119118 A1           | 29-08-2002          |
|   |                     | US 2002161199 A1           | 31-10-2002          |
|   |                     | US 2002156006 A1           | 24-10-2002          |
|   |                     | US 2002169284 A1           | 14-11-2002          |
|   |                     | US 2002072496 A1           | 13-06-2002          |
|   |                     | US 2002142961 A1           | 03-10-2002          |
|   |                     | US 2002072067 A1           | 13-06-2002          |
|   |                     | US 2002072092 A1           | 13-06-2002          |
| -----                                     |                     |                            |                     |
| WO 0053756                                | A                   | 14-09-2000                 |                     |
|   |                     | AU 1748200 A               | 19-06-2000          |
|   |                     | AU 1749900 A               | 12-07-2000          |
|   |                     | AU 2192800 A               | 12-07-2000          |
|   |                     | AU 2224800 A               | 28-09-2000          |
|   |                     | AU 2399300 A               | 28-09-2000          |
|   |                     | AU 2495200 A               | 28-09-2000          |
|   |                     | AU 2596700 A               | 28-09-2000          |

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 01/21735

| Patent document<br>cited in search report | Publication<br>date | Patent family<br>member(s) | Publication<br>date |
|---|---------------------|----------------------------|---------------------|
| WO 0053756                                | A                   | AU 2600800 A               | 28-09-2000          |
|   |                     | AU 2879400 A               | 31-07-2001          |
|   |                     | AU 2883600 A               | 28-09-2000          |
|   |                     | AU 3072199 A               | 27-09-1999          |
|   |                     | AU 3107700 A               | 28-09-2000          |
|   |                     | AU 3381600 A               | 28-09-2000          |
|   |                     | AU 3514400 A               | 28-09-2000          |
|   |                     | CA 2321677 A1              | 16-09-1999          |
|   |                     | EP 1173563 A1              | 23-01-2002          |
|   |                     | EP 1159419 A1              | 05-12-2001          |
|   |                     | EP 1220905 A2              | 10-07-2002          |
|   |                     | EP 1135485 A2              | 26-09-2001          |
|   |                     | EP 1141284 A2              | 10-10-2001          |
|   |                     | EP 1159422 A1              | 05-12-2001          |
|   |                     | EP 1141289 A2              | 10-10-2001          |
|   |                     | US 2002119130 A1           | 29-08-2002          |
|   |                     | WO 0053753 A2              | 14-09-2000          |
|   |                     | WO 0053754 A1              | 14-09-2000          |
|   |                     | WO 0053755 A2              | 14-09-2000          |
|   |                     | WO 0153486 A1              | 26-07-2001          |
|   |                     | WO 0053756 A2              | 14-09-2000          |
|   |                     | WO 0053757 A2              | 14-09-2000          |
|   |                     | WO 0053758 A2              | 14-09-2000          |
|   |                     | US 2002127584 A1           | 12-09-2002          |
|   |                     | US 2002094416 A1           | 18-07-2002          |
|   |                     | WO 0032221 A2              | 08-06-2000          |
|   |                     | WO 0053750 A1              | 14-09-2000          |
|   |                     | WO 0037638 A2              | 29-06-2000          |
|   |                     | WO 0037640 A2              | 29-06-2000          |
|   |                     | WO 0053751 A1              | 14-09-2000          |
|   |                     | WO 0053752 A2              | 14-09-2000          |
|   |                     | US 2002119118 A1           | 29-08-2002          |
|   |                     | US 2002161199 A1           | 31-10-2002          |
|   |                     | US 2002156006 A1           | 24-10-2002          |
|   |                     | US 2002169284 A1           | 14-11-2002          |
|   |                     | US 2002072496 A1           | 13-06-2002          |
|   |                     | US 2002142961 A1           | 03-10-2002          |
|   |                     | US 2002072067 A1           | 13-06-2002          |
|   |                     | US 2002072092 A1           | 13-06-2002          |
| WO 0200690                                | A                   | 03-01-2002                 | US 2002042367 A1    |
|   |                     |                            | 11-04-2002          |
|   |                     |                            | US 2002010137 A1    |
|   |                     |                            | 24-01-2002          |
|   |                     |                            | US 2002106743 A1    |
|   |                     |                            | 08-08-2002          |
|   |                     |                            | US 2002052027 A1    |
|   |                     |                            | 02-05-2002          |
|   |                     |                            | US 2002058309 A1    |
|   |                     |                            | 16-05-2002          |
|   |                     |                            | US 2002102723 A1    |
|   |                     |                            | 01-08-2002          |
|   |                     |                            | AU 6871401 A        |
|   |                     |                            | 08-01-2002          |
|   |                     |                            | AU 7885201 A        |
|   |                     |                            | 08-01-2002          |
|   |                     |                            | WO 0200690 A2       |
|   |                     |                            | 03-01-2002          |
|   |                     |                            | WO 0200711 A2       |
|   |                     |                            | 03-01-2002          |
|   |                     |                            | AU 6531101 A        |
|   |                     |                            | 17-12-2001          |
|   |                     |                            | AU 7197301 A        |
|   |                     |                            | 05-02-2002          |
|   |                     |                            | AU 7315001 A        |
|   |                     |                            | 30-01-2002          |
|   |                     |                            | WO 0193983 A1       |
|   |                     |                            | 13-12-2001          |
|   |                     |                            | WO 0208288 A2       |
|   |                     |                            | 31-01-2002          |
|   |                     |                            | WO 0208284 A2       |
|   |                     |                            | 31-01-2002          |
|   |                     |                            | AU 1916701 A        |
|   |                     |                            | 16-07-2001          |
|   |                     |                            | AU 2055401 A        |
|   |                     |                            | 12-06-2001          |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 01/21735

| Patent document<br>cited in search report |   | Publication<br>date |    | Patent family<br>member(s) | Publication<br>date |
|---|---|---------------------|----|----------------------------|---------------------|
| WO 0200690                                | A |                     | AU | 6391000 A                  | 19-02-2001          |
|   |   |                     | AU | 6802801 A                  | 24-09-2001          |
|   |   |                     | AU | 6901800 A                  | 12-06-2001          |
|   |   |                     | EP | 1244784 A2                 | 02-10-2002          |
|   |   |                     | EP | 1250426 A2                 | 23-10-2002          |
|   |   |                     | EP | 1259614 A2                 | 27-11-2002          |
|   |   |                     | WO | 0140464 A1                 | 07-06-2001          |
|   |   |                     | WO | 0149715 A2                 | 12-07-2001          |
|   |   |                     | WO | 0140466 A2                 | 07-06-2001          |
|   |   |                     | WO | 0168848 A2                 | 20-09-2001          |
|   |   |                     | US | 2002127584 A1              | 12-09-2002          |
|   |   |                     | US | 2002094416 A1              | 18-07-2002          |
|   |   |                     | US | 2002160374 A1              | 31-10-2002          |
|   |   |                     | US | 2002146709 A1              | 10-10-2002          |
|   |   |                     | US | 2002132240 A1              | 19-09-2002          |
|   |   |                     | US | 2002142958 A1              | 03-10-2002          |
|   |   |                     | US | 2002150976 A1              | 17-10-2002          |
|   |   |                     | US | 2002132981 A1              | 19-09-2002          |
|   |   |                     | US | 2002165143 A1              | 07-11-2002          |
|   |   |                     | US | 2002156004 A1              | 24-10-2002          |
|   |   |                     | US | 2002142419 A1              | 03-10-2002          |
|   |   |                     | US | 2002102647 A1              | 01-08-2002          |
|   |   |                     | US | 2002110859 A1              | 15-08-2002          |
|   |   |                     | US | 2002142959 A1              | 03-10-2002          |
|   |   |                     | US | 2002115145 A1              | 22-08-2002          |
|   |   |                     | US | 2002132768 A1              | 19-09-2002          |
|   |   |                     | US | 2002127643 A1              | 12-09-2002          |
|   |   |                     | US | 2002156006 A1              | 24-10-2002          |
|   |   |                     | US | 2002169284 A1              | 14-11-2002          |
|   |   |                     | US | 2002072496 A1              | 13-06-2002          |
|   |   |                     | US | 2002142961 A1              | 03-10-2002          |
|   |   |                     | US | 2002072067 A1              | 13-06-2002          |
| -----                                     |   |                     |    |                            |                     |
| WO 0032221                                | A | 08-06-2000          | AU | 736506 B2                  | 26-07-2001          |
|   |   |                     | AU | 1602999 A                  | 16-06-1999          |
|   |   |                     | AU | 1748200 A                  | 19-06-2000          |
|   |   |                     | AU | 2474700 A                  | 19-06-2000          |
|   |   |                     | AU | 3107000 A                  | 19-06-2000          |
|   |   |                     | CA | 2311640 A1                 | 10-06-1999          |
|   |   |                     | EP | 1037979 A2                 | 27-09-2000          |
|   |   |                     | EP | 1135485 A2                 | 26-09-2001          |
|   |   |                     | EP | 1135491 A2                 | 26-09-2001          |
|   |   |                     | EP | 1135495 A2                 | 26-09-2001          |
|   |   |                     | JP | 2002505850 T               | 26-02-2002          |
|   |   |                     | JP | 2002531092 T               | 24-09-2002          |
|   |   |                     | US | 2002127584 A1              | 12-09-2002          |
|   |   |                     | WO | 0032776 A2                 | 08-06-2000          |
|   |   |                     | WO | 0032221 A2                 | 08-06-2000          |
|   |   |                     | WO | 0032778 A2                 | 08-06-2000          |
|   |   |                     | US | 2002058309 A1              | 16-05-2002          |
|   |   |                     | US | 2002160374 A1              | 31-10-2002          |
|   |   |                     | US | 2002146709 A1              | 10-10-2002          |
|   |   |                     | US | 2002132240 A1              | 19-09-2002          |
|   |   |                     | US | 2002142958 A1              | 03-10-2002          |
|   |   |                     | US | 2002150976 A1              | 17-10-2002          |
|   |   |                     | US | 2002132981 A1              | 19-09-2002          |
|   |   |                     | US | 2002165143 A1              | 07-11-2002          |
|   |   |                     | US | 2002156004 A1              | 24-10-2002          |

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 01/21735

| Patent document<br>cited in search report | Publication<br>date | Patent family<br>member(s) | Publication<br>date |
|---|---------------------|----------------------------|---------------------|
| WO 0032221 A                              |                     | US 2002142419 A1           | 03-10-2002          |
|   |                     | US 2002102647 A1           | 01-08-2002          |
|   |                     | US 2002110859 A1           | 15-08-2002          |
|   |                     | US 2002142959 A1           | 03-10-2002          |
|   |                     | US 2002115145 A1           | 22-08-2002          |
|   |                     | US 2002132768 A1           | 19-09-2002          |
|   |                     | US 2002127643 A1           | 12-09-2002          |
|   |                     | US 2002072496 A1           | 13-06-2002          |
|   |                     | US 2002142961 A1           | 03-10-2002          |
|   |                     | US 2002072067 A1           | 13-06-2002          |
|   |                     | US 2002072092 A1           | 13-06-2002          |
|   |                     | US 2002072497 A1           | 13-06-2002          |
|   |                     | US 2002103125 A1           | 01-08-2002          |
|   |                     | US 2002123463 A1           | 05-09-2002          |
|   |                     | US 2002132252 A1           | 19-09-2002          |
|   |                     | US 2002127576 A1           | 12-09-2002          |
|   |                     | US 2002132253 A1           | 19-09-2002          |
|   |                     | US 2002160384 A1           | 31-10-2002          |
|   |                     | AU 1749900 A               | 12-07-2000          |
|   |                     | AU 2192800 A               | 12-07-2000          |
|   |                     | AU 2224800 A               | 28-09-2000          |
| WO 0015792 A                              | 23-03-2000          | AU 5920099 A               | 03-04-2000          |
|   |                     | CA 2341767 A1              | 23-03-2000          |
|   |                     | EP 1112361 A2              | 04-07-2001          |
|   |                     | WO 0015792 A2              | 23-03-2000          |
|   |                     | AU 9484398 A               | 05-04-1999          |
|   |                     | US 2002160374 A1           | 31-10-2002          |
|   |                     | US 2002146709 A1           | 10-10-2002          |
|   |                     | US 2002132240 A1           | 19-09-2002          |